UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF OHIO
EASTERN DIVISION

IN RE: NATIONAL PRESCRIPTION OPIATE LITIGATION	)	MDL No. 2804
This document relates to:	)	Case No. 17-md-2804
The County of Cuyahoga v. Purdue Pharma L.P., et al., Case No. 17-OP-45004 (N.D. Ohio)	)	Hon. Dan Aaron Polster
The County of Summit, Ohio, et al. v. Purdue Pharma L.P. et al., Case No. 180OP-45090 (N.D. Ohio)	)	

REPORT OF CARL C. PECK, M.D.

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I. BACKGROUND AND QUALIFICATIONS

I am a board-certified physician in internal medicine and clinical pharmacology. I attended the University of Kansas as both an undergraduate and medical student, receiving a bachelor's degree in mathematics and chemistry before earning my medical degree in 1968. Between undergraduate and medical school, I received a Fulbright Grant and studied physical chemistry at the Technische Hochschule in Stuttgart, Germany.

During my professional career as an internist and physician-scientist, I have held academic research and teaching positions at several institutions, including Clinical Assistant Professor and Adjunct Professor of Medicine and Bioengineering and Therapeutic Sciences at the University of California San Francisco ("UCSF"), and Chief of the Division of Blood Research at the Letterman Army Institute of Research, Professor and Director of the Division of Clinical Pharmacology at the Uniformed Services University of the Health Sciences, as well as Professor of Pharmacology at Georgetown University. In these positions, I conducted and analyzed many human clinical trials.

I served in the U.S. Army Medical Corps and Medical Research and Development Command from 1967 to 1990, achieving the rank of Colonel. From 1980 to 1987, I was assigned as Consultant in Clinical Pharmacology to the Army Surgeon General. In 1990, I transferred to the U.S. Public Health Service, where I held the rank of Rear Admiral and was appointed Assistant Surgeon General of the United States. In these roles, I advised the Surgeon General on the safety of the nation's drug supply for emergency use in military and civilian disaster situations.

I was named Director of the Center for Drug Evaluation and Research ("CDER") at the Food and Drug Administration ("FDA") in 1987 and served in that position until

1993, when I retired from government service after 26 years. As the Director of CDER, I supervised over 1700 scientists, managers and associated FDA staff. My responsibilities included establishing and enforcing standards of guidance, review and approval or rejection of new medical products, safety of all marketed products, and advertising and promotional practices of pharmaceutical manufacturers.

I have testified before Congress on numerous occasions, explaining FDA policies and decisions to the public in advisory committee meetings, scientific conferences, and in press interviews. In my FDA position, I reviewed and commented on the sufficiency of the studies that were being performed to support Investigational New Drug applications ("INDs") and New Drug Applications ("NDAs"), including clinical trials and stability studies. During my six years at CDER, I reviewed, commented or rendered decisions on data relating to more than 500 INDs, NDAs, policy documents, requests for drug information from Members of Congress and the media, and Citizen Petitions.

In late 1993, I was appointed the Honorary Boerhaave Professor at the University of Leiden in the Netherlands, where I taught and researched human drug development and regulation at the Leiden-Amsterdam Center for Drug Research.

Following my time in Europe, in 1994, I became Professor of Pharmacology and the Founding Director of the Center for Drug Development Science ("CDDS") at Georgetown University in Washington, DC. In 2004, the Center was transferred to the UCSF and I became the Director of the CDDS in the School of Pharmacy at UCSF, and Professor in the Department of Bioengineering and Therapeutic Sciences at UCSF. As an academic research, education, public policy, and technical assistance center, CDDS permitted the continuation of my career-long study of scientific and regulatory methods for

evaluating the effectiveness and safety of new medicines. In 2006, I retired from the directorship of CDDS. Since then, I have continued teaching at the UCSF as an Adjunct Professor.

I co-founded the UCSF-American (2007) and Chinese (2009) Courses in Drug Development and Regulatory Science ("ACDRS, CCDRS"), which are Executive Masters level courses in advanced drug development for experienced industry scientists and regulatory agency scientists and reviewers. I served as a founding member of the Executive and Planning Committees of the ACDRS, CCDRS. I also served as a member of the Advisory Board for the European Center for Pharmaceutical Medicine. In addition, I served on Advisory Board for PharmaTrain, and the Innovative New Medicines Initiative (IMI) Master of Pharmaceutical Medicine degree program funded by the European Commission.

Throughout my professional career, I have published over 150 original scientific papers as well as a book and several book chapters. For over 40 years, I have also been an active journal reviewer for multiple scientific publications, including Clinical Pharmacology and Therapeutics. I have also served as a member of the Publications Committee of the American Society for Clinical Pharmacology and Therapeutics ("ASCPT"), and I have reviewed research manuscripts submitted for publication in journals sponsored by ASCPT. I served on the ASCPT Board of Directors for many years prior to being elected President in 1998.

I am the Founder and Chairman of NDA Partners LLC, which is an international consulting company that provides scientific and regulatory advice and services to scientists and entrepreneurs in private industry as well as to government agencies such as the

Department of Defense. NDA Partners assists companies in understanding and meeting the FDA's high scientific standards and requirements, and it supports various aspects of companies' engagements with the FDA during the IND, NDA, and post-approval phases. Our services include advising on clinical and stability study designs as well as clinical trial analysis, interpretation, and communications with the FDA. While at NDA Partners, I have personally consulted on more than 200 INDs and NDAs. I have helped companies to develop strategies for evaluating the clinical pharmacology, safety, and effectiveness of new drugs in order to satisfy the high standards of the FDA. I have also served on numerous Science Advisory Boards and several Boards of Directors of biopharmaceutical companies.

My honors and awards include the Department of Army Research and Development Award for contributions to the multi-center cooperative evaluations of the CPDA-1 blood preservative system (1978), Army Meritorious Service Medal (1980), the Defense Superior Service Medal (1988), the FDA Distinguished Career Service Award (1993), the FDA Distinguished Alumnus Award (1999), and an Honorary Doctorate Degree from Uppsala University in Sweden for "outstanding contributions to the science of drug development" (2002). More recently, I was awarded the Henry W. Elliott Distinguished Service Award by the ASCPT (2009), the ASCPT Gary Neil Prize for Innovation in Drug Development (2012), and the ASCPT Sheiner-Beal Pharmacometrics Award (2017).

A more complete description of my qualifications and a list of my publications appear in my attached curriculum vitae at Exhibit B.

A list of all cases in which, during the previous four years, I testified as an expert at trial or deposition appears at Exhibit C.

I understand that Allergan Finance, LLC, Allergan plc, Allergan Sales, LLC, and Allergan USA, Inc. ("Allergan"), among others, have been named Defendants in *In re: National Prescription Opiate Litigation* (MDL No. 2804), including in cases brought by the County of Cuyahoga and the County of Summit (the "Track One Plaintiffs").

Allergan has asked me to evaluate and provide opinions regarding these cases. Allergan has also asked me to analyze expert reports served by the Track One Plaintiffs as well as to testify regarding the conclusions I reached. In this report, I respond to certain opinions expressed by Plaintiff experts David Egilman and David Kessler.

I am being compensated for my time at my usual rate of $650 per hour. My compensation is in no way contingent upon my testimony or the outcome of the case.

I reserve the right to supplement this report or to respond to any additional opinions or arguments presented by Plaintiffs or Plaintiffs' proffered experts. If asked to testify at trial or in any other hearing, I may use demonstrative and summary exhibits. I have yet to prepare any such exhibits, but I expect to do so in accordance with the Court's scheduling orders.

II. MATERIALS CONSIDERED

I have reviewed the operative Complaints brought by the Track One Plaintiffs and understand that they allege a number of claims against Allergan that primarily relate to Allergan's ownership of opioid pain medications.[1] The Complaints reference, among medications sold by other Defendants, two opioid medications that Allergan owns, Kadian® and Norco®. Kadian® is an extended-release, long-acting morphine sulfate

[1] *See* Third Amended Complaint and Jury Demand, *The County of Summit, Ohio v. Purdue Pharma, L.P., et al.*; Second Amended Corrected Complaint, *The County of Cuyahoga, Ohio v. Purdue Pharma L.P., et al.*

product that was approved by the FDA under an NDA in 1997. The Kadian® NDA, which was sponsored by an unaffiliated company, was acquired by a former Allergan Finance, LLC affiliate in 2009. Norco® is an immediate release hydrocodone and acetaminophen product that was originally approved by the FDA under two Abbreviated New Drug Applications ("ANDAs") in 1997.

In forming my opinions, I have considered, among others, materials such as Kadian® and Norco® regulatory files, correspondence with the FDA about Kadian® and Norco®, documents related to the promotion of opioids, documents related to training materials for Kadian®, deposition transcriptions and exhibits, reports and related materials of several of the Track One Plaintiffs' experts, and other documents and materials cited throughout this report. In addition to those cited throughout, other materials that I have considered in preparing this Report are listed in Exhibit A.

III. SUMMARY OF CONCLUSIONS

Based on my knowledge, skill, education, training, and experience in clinical pharmacology, drug development and regulation—including as a former Director of the FDA's CDER—as well as my analysis of the materials described above, I have formulated the opinions that I have set out in this Report. Those include the following:

- The FDA plays a critical role in reviewing, approving and monitoring the safety and efficacy of medicine products during their entire life-span, including during development, upon NDA submission, and post-approval.
- This is the case for Allergan's opioid analgesic products Kadian® and Norco®, both of which were approved as safe and effective by the FDA.

- The FDA has long regulated and permitted the use of prescription opioids; in fact, it continues to approve prescription opioids as safe and effective.
- The FDA's ongoing oversight of prescription opioids continues after their approval. For example, the FDA has imposed post-approval requirements on Allergan and other application holders to further study and monitor the risks and benefits of prescription opioids. In addition, the FDA has considered a number of opioid-related Citizen Petitions, and continually monitors reported adverse events related to prescription opioids medications.
- Allergan's response to a 2010 Warning Letter from FDA was prompt, comprehensive and approved by FDA. The FDA took no further action, which indicates that it was satisfied with Allergan's response.
- At all times since Allergan acquired Kadian® in late December 2008, its physician labeling has fully and appropriately warned of its risks. Norco®'s labeling also appropriately communicated its risks to prescribers. Further, both Kadian® and Norco® have Medication Guides that provide clear risk information to patients.
- Allergan's participation in the FDA-approved Opioid Analgesic REMS for extended-release, long-acting opioids has resulted in the provision of additional risk/benefit information for prescribers and patients.
- Dr. Kessler's and Dr. Egilman's opinions as they relate to Allergan are inaccurate, incomplete and otherwise flawed.

IV. FDA AND ITS REGULATORY FRAMEWORK

A. The FDA plays a critical role in monitoring the safety and efficacy of medicine products in the U.S.

The FDA is the government agency responsible for assuring that certain products sold in the United States—primarily foods, drugs, cosmetics, biologics, tobacco, veterinary, and medical devices—are safe, effective, and labeled with adequate directions so they can be used for their intended purpose(s).[2] The FDA administers a body of law through regulations, guidelines and guidances that authorize the FDA to provide assurance to the citizens of the United States that the products that the FDA is responsible for are safe and effective and meet the requirements of applicable laws.

The FDA accomplishes its mission via a nationwide staff of experts that review products prior to marketing, oversee clinical trial design and execution, inspect manufacturing and testing facilities, monitor products after approval, and investigate inquiries from Congress, consumer groups, pharmaceutical companies and others, among other roles and responsibilities.

Currently, the approximately $5 billion budget of the FDA supports approximately 17,500 employees, including those in the Commissioner's Office and nine Centers and Offices. Forty-five percent of the FDA's budget comes from user fees, paid by pharmaceutical developers, while the remainder comes from the federal budget authorization.

Although the FDA serves an essential and unique function in safeguarding the health and safety of our citizens, recourse is available in the event of a disagreement with an FDA determination. For example, a manufacturer that has been denied approval of an

[2] https://www.fda.gov/AboutFDA/WhatWeDo/default.htm

application to the FDA may appeal according to formal dispute resolution procedures, and citizens may report safety concerns or wrongdoing and petition the FDA to take action by filing a citizen petition.[3]

B. The FDA carefully reviews each medication's New Drug Application, which it must approve before the medication can be sold.

The FDA keys its review of an NDA on its required format and content of the submission document package. The NDA format requirements have changed over the years from that implemented in the "NDA Rewrite" in the mid-1980s to the Common Technical Document ("CDT")[4] format first adopted in 2001 by FDA via its involvement in activities of the International Conference on Harmonization of Technical Requirements for Human Use ("ICH").[5] Further, the content of the NDA comprises data, analyses and conclusions derived from the scientific findings that are documented during the drug development process. Thus, to understand how FDA reviews an NDA, it is important to know of the sequence and processes involved in regulated drug development.

In the United States, the development of new medicines to treat human diseases is a highly regulated, complex and arduous endeavor.[6] It involves a number of steps and stages during which the applicant (*i.e.*, the company developing the new medication) and the FDA work closely together to design and carry out testing and other procedures. The ultimate regulatory judgement in cases where the new product is approved is a

[3] *See* 21 CFR § 10.30.

[4] M4 Organization of the Common Technical Document for the Registration of Pharmaceuticals for Human Use Guidance for Industry. October 2017, available at https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073257.pdf.

[5] Justina A. Molzon. ICH–Its History, Evolution, Achievements and Challenges, available at http://www.asq509.org/ht/a/GetDocumentAction/i/101605.

[6] The Drug Development Process, available at https://www.fda.gov/forpatients/approvals/drugs/.

determination by the FDA that the new product is safe and effective for its intended use. No new products—including opioid pain medications—can be sold or prescribed in the United States unless and until the FDA makes that determination.

Preclinical testing. Prior to testing in humans, a candidate new drug must undergo extensive chemical and biological investigations, required by FDA, to document its chemical structure, impurities, stability, and pharmacological and toxicological effects in animals. These studies must be conducted using FDA defined "Good Laboratory Practices."[7] Two or more years are required to complete these preclinical evaluations. Preclinical evaluations include numerous laboratory *in vitro*[8] and animal pharmacology experiments, which include documentation of the pharmacokinetics, toxicokinetics, single and repeat dose toxicity, genotoxicity, carcinogenicity, and reproductive toxicity.[9] The required preclinical studies also include single and multiple dose administrations in two rodent and a non-rodent animal species of a wide range of dosages. The objectives of these mandatory tests are to affirm the potential for beneficial effects in human disease as well as to identify potential harmful effects to minimize in later human clinical trials. Further, determination of toxic and non-toxic dosages in animals serves as the basis for selection of safe doses to use in the first human trial.

Investigational New Drug submission. Upon completion of these pre-clinical tests, sponsors of new medicines submit an IND to the FDA summarizing non-clinical investigations.

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[7] *See* 21 CFR 58.

[8] *In vitro* refers to chemistry, biology and pharmacology testing using experimental materials in a laboratory setting that do not involve direct testing in living animals or humans.

[9] FDA Guidance for Industry, *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals* (January 2010), available at https://www.fda.gov/downloads/drugs/guidances/ucm073246.pdf.

The IND also includes the proposed protocol for the first human study.[10] The FDA must review and approve this protocol before the first human study may begin.[11] Before the FDA approves the protocol, it conducts a penetrating review by a team of chemists, pharmacologists,[12] toxicologists,[13] microbiologists,[14] and physicians. FDA scientists apply rigorous standards to this review in order to assure that safe doses of the new medicine are used to minimize harm to human subjects who volunteer to participate in clinical trials, and to assure that the proposed first trial will be informative.

Phase 1. The next steps in the new drug approval process are three phases of testing in humans.[15] Phase 1 trials are performed to establish tolerated doses, among other information. Phase 2 trials are proof of concept and dose-response investigations. Phase 3 trials provide definitive proof of effectiveness, and they complete the safety evaluation of the new medicine.

Phase 1 trials—the very first human trials of a new medicine—usually involve normal, healthy volunteers. These volunteers' carefully-monitored responses to increasing single and multiple doses of the new drug (and placebo) provide critical information about acute symptomatic side effects, such as nausea, vomiting, diarrhea, appetite, headache,

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[10] *See* 21 C.F.R. § 312.23.

[11] *See* Policies and Procedures - FDA Office of New Drugs - *Good Review Practice: Good Review Management Principles and Practices for Effective IND Development and Review*, available at https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/UCM349907.pdf

[12] Chemist reviewers evaluate the chemical constituents of drugs, including the active and inactive ingredients, as well as any impurities or contaminants that may be present due to the manufacturing processes. Pharmacologists assess the potential beneficial effects of the active ingredients of a new drug in in vitro tests and on the body and behavior of test animals.

[13] Toxicologists evaluate the potentially harmful (toxic) effects the active ingredients of a new drug in in vitro tests and on the body and behavior of test animals.

[14] Microbiologists review the potential for bacterial and viral contamination of drug formulations.

[15] *See* 21 C.F.R. § 312.21.

dizziness, gait, sedation, anxiety, mood, and other reactions.[16] Blood pressure, pulse, and electrocardiogram measurements, along with various laboratory tests on blood and urine, provide information regarding dose-related effects on each subject's gastro-intestinal (esophagus, stomach, intestines, liver), cardiovascular, renal, hematological, respiratory, neurological and central nervous systems.

During Phase 1 trials, measurements of the concentrations of the new medicine and its metabolites in blood and urine at various times provide data for characterization of the time-course of the medicine in the body. These observations comprise the pharmacokinetics and metabolism of the medicine, reflecting what the body does to the medicine. They also provide information regarding pathways of metabolism and elimination involving the liver and kidney.

Phase 2. The information gained in Phase 1 studies is important in part because it can be used to identify safe dosage regimens for the Phase 2 trials, such as what dose to provide to subjects, in what dosing interval, and for what duration. When sufficient knowledge of tolerability and other relevant properties of the new medicine is gained in Phase 1 studies to identify these safe dosage regimens, the first Phase 2 trial (2a) in patients is planned and initiated. The primary purpose of Phase 2a trials is to provide preliminary verification, under closely monitored conditions, of the expected beneficial effect(s) of the new medicine in patients with the target medical condition—in other words, whether the new drug shows promise of working in patients.

[16] *See* Presentation re *Clinical Pharmacology 1: Phase 1 Studies and Early Drug Development* (G. Gieser) (2012), available at https://www.fda.gov/downloads/training/clinicalinvestigatortrainingcourse/ucm340007.pdf.

In Phase 2a trials, randomized, blinded treatments comprising several doses of the new medicine and placebo are administered to a modest number of patient volunteers in one, or several, trials to ascertain symptom improvement or relief, or biomarker responses that may reflect disease improvements. Phase 2a trials are often called "proof-of-concept" ("POC") studies, because, if indicative of potential benefit to the patients who are subjects in the study, they provide motivation and basis for one or more subsequent, Phase 2b trials.

The principal purpose of Phase 2b trials is to identify a safe, likely to prove effective, dosage regimen(s) to employ in the Phase 3 program. Phase 2b trials also provide resolution of other safety/effectiveness issues such as timing of treatment and further selection of the target population for the medication.

Phase 3. The Phase 3 trial program commonly comprises two or more large randomized, blinded trials. That they are randomized means that treatments in the trials are assigned to patients in a random fashion. That they are blinded means that during the trial, patients and investigators are not made aware of the specific treatment selected for each patient in order to prevent biasing trial execution, outcomes or interpretation. These two or more Phase 3 trials aim to confirm the effectiveness and safety of the to-be-marketed dosage regimen(s), as compared with placebo or another effective treatment of patients with the target disease. Phase 3 trials can include as many as hundreds to thousands of patients in multiple clinical trial sites. They are conducted per a common protocol that the FDA reviews in conjunction with the end-of-Phase 2 meeting with the sponsor.[17]

[17] *See Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products Guidance for Industry* (2017), available at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM590547.pdf.

NDA submission and review. After completion and analysis of the results of Phase 3 trials, the entire database of chemistry, manufacturing, in vitro and animal pharmacology and toxicology, and Phase 1, 2, and 3 trial results (raw data tables, case report forms, and clinical study reports) are incorporated in the NDA submitted to FDA for review. At this point, the applicant submits the NDA to the FDA for its consideration.

Within 60 days of receipt of the NDA, a team of FDA scientists—including chemists, basic and clinical pharmacologists, toxicologists, microbiologists, pharmacometricians, statisticians and physicians—scan the NDA for completeness and reviewability, deciding whether to accept the NDA for formal review.[18] If accepted, the FDA team commences a thorough and critical review, which can last many months, of all aspects of the NDA database, undertaking re-analyses of raw data, in order to independently critique the sponsor's findings of effectiveness and safety. Once the primary team has concluded its review and recommendations that the FDA take one of several actions—including approval (with or without post-marketing requirements), or approvability with requirement for further studies—secondary reviews within the division and at the division director level are undertaken. The final decision is made after additional review by the Office Director in which the division resides.

FDA reviews an NDA in order to confirm that the evidence submitted is sufficient to demonstrate safety and effectiveness, and also to ensure that the data submitted are complete and accurate. The FDA's review can take months or years and may involve

[18] *See Refuse to File: NDA and BLA Submissions to CDER Guidance for Industry* (2017), available at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM588242.pdf.

several cycles of NDA submission and FDA review, multiple requests by FDA for responses to questions and for more data, and submissions of amendments to the NDA. As set forth more fully below, the FDA also carefully reviews the proposed labeling.

A new medicine must be found to be safe and effective when used in accordance with the proposed labeling in order to be approved.[19] Safety and efficacy for the approved indications must be established by scientifically rigorous, well-controlled clinical studies. However, because all medicines have risks, FDA approval does not mean a medicine is absolutely safe, or has no risks or side effects. Rather, FDA approval means that the FDA has determined that the benefits of the product for the category of patients for whom the medicine is intended have been shown in pre-approval trials to outweigh the risks when the product is used in accordance with the approved labeling.[20]

CDER is the part of the FDA that reviews NDAs. CDER employs more than 5,000 staff and is organized into several groups, called offices.[21] One group is responsible for the review of NDAs, another for the review of generic drug applications, and another for the review of "over-the-counter" drugs. Additionally, there are offices and divisions concerned with compliance and enforcement, the advertising and promotion of prescription drugs, the monitoring of adverse events in marketed drugs, and research and management support.

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[19] *See* 21 U.S.C. § 355; *The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective*, available at https://www.fda.gov/drugs/resourcesforyou/consumers/ucm143534.htm.

[20] *See, e.g.*, *About FDA Product Approval*, available at https://www.fda.gov/newsevents/productsapprovals/ucm106288.htm; *Development & Approval Process (Drugs)*, available at https://www.fda.gov/drugs/developmentapprovalprocess/default.htm.

[21] *See About the Center for Drug Evaluation and Research*, available at https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/default.htm.

CDER's review of NDAs is comprehensive and thorough. It is accomplished by subject matter experts, well-versed in each aspect of the proposed medication. Upon submission to the FDA, each NDA is assigned to a particular reviewing division within one of the Offices of New Drug Evaluation, such as the Office of Antimicrobial Products, Offices of Drug Evaluation I-IV, and Office of Hematology and Oncology Drug Products.[22] The component parts of the NDA are distributed to reviewers trained in specific disciplines within each appropriate review division.

For example, the Chemistry, Manufacturing, and Controls ("CMC") portion of the NDA is assigned to a team of Ph.D. chemists who review the product in terms of its chemistry, formulation, and its characteristics in terms of stability, strength, purity and quality.[23] In addition, the chemistry and manufacturing team reviews the assay methods in order to ensure that the intermediate product forms which occur during manufacture, as well as the final product form, meet established specifications. This group also examines the product and manufacturing data for any contaminants, variable polymorphic structures or any other characteristics that might affect safe and uniform product production.

The clinical pharmacology and biopharmaceutics portions of the NDA, are reviewed by a group of Ph.D., Pharm.D. and M.D. clinical pharmacologists and biopharmaceutical scientists.[24] These reviewers undertake evaluations of the product

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[22] *See* Office of New Drugs, available at https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm184426.htm.

[23] *See* Chemistry Review of Question-based Review (QbR) Submissions. MAPP 5015.00. https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/UCM423752.pdf.

[24] *See Clinical Pharmacology Review of New Molecular Entity (NME) New Drug Applications (NDAs) and Original Biologics License Applications (BLAs)*, MAPP 4000.4 Rev 1, available at https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/UCM073007.pdf.

formulation, and the pharmacokinetics and metabolism of the medicine (*i.e.*, what the body does to the medicine, including how the medicine is absorbed, distributed, metabolized and eliminated from the body). In addition, the pharmacodynamics of the medicine are evaluated (*i.e.*, measurable indicators on what the medicine does to various function in the body). Other issues considered in this part of the NDA review include drug interactions, specific effects on heart rhythm, and focus on the pharmacokinetics and bioavailability of the product in terms of rate of absorption and excretion and its bioequivalence[25] with earlier forms that may have been used in clinical studies are functionally the same.

The pharmacology/toxicology portion of the NDA is assigned to a team of Ph.D. toxicologists and pharmacologists. This team reviews the preclinical studies in great detail, looking for safety signals from *in vitro* and animal studies of the product ingredients that can alert the FDA to possible problems with the product in clinical studies and future clinical use.

The clinical portion of the NDA is first assigned to a physician, designated as the clinical reviewer.[26] The clinical reviewer critically evaluates the original protocols and the summary data obtained from product studies. The clinical reviewer also evaluates the raw clinical data, including to confirm that the protocol was followed, that patients admitted to the study met protocol criteria, and that the pivotal clinical trials were adequate and well-controlled and conducted. This physician scientist pays particular attention to serious adverse medical outcomes, deaths, and interactions with concomitant therapy. The FDA

[25] Bioequivalence refers to a pharmacokinetic testing procedure for assuring that two drug products are expected to have the same safety and efficacy effects, despite differences in the product characteristics.

[26] *See* Good Review Practice: Clinical Review Template, MAAP 6010.3, available at https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/UCM080121.pdf.

performs these analyses to be certain that the product conforms with standards set forth in governing regulations, and in order to ensure that the label is completely accurate.

Each reviewer—*e.g.*, the clinical reviewer—prepares a written summary of his or her review and recommendations. These summaries then go through several layers of review. First, they are reviewed by a supervisor in each discipline, each of whom writes a separate review, referencing the subordinates review. The supervisory review is followed by the next level review by the Division Director, and finally, the Office Director. An overall summary will be written by the approving official, either the Division or Office Director. This summary, sometime called the "Summary Basis of Approval," critically references notable findings, conclusions, and recommendations of all prior reviews, and includes the approving official's conclusions as to the legal and scientific basis for the approval. The collection of these reviews, along with the overall summary, becomes the FDA's basis for final action on the NDA.

The various FDA reviewers may initially disagree on whether the NDA has met the applicable standards, in which case these critical scientists engage in further study and scientific debate.[27] In some cases, managers convene meetings to debate and achieve a consensus when reviewers cannot resolve their differences on their own. Ultimately, the senior-most CDER official with approval authority, taking into account all reviewers' opinions along with his or hers as well, makes a final informed decision regarding whether the NDA should be approved.

[27] *See Scientific / Regulatory Dispute Resolution for Individuals Within a Management Chain*, MAPP 4251.1 Rev. 1, available at https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/StaffPoliciesandProcedures/UCM073557.pdf.

FDA sometimes involves one of its many standing outside advisory committees in the review process after internal FDA review is completed. In the FDA's own words, the "committees are established to provide functions which support the FDA's mission of protecting and promoting the public health, while meeting the requirements set forth in the Federal Advisory Committee Act. Committees are either mandated by statute or established at the discretion of the Department of Health and Human Services."[28]

In addition, the FDA's field force often conducts a "pre-approval" inspection to assure that the manufacturing facility and processes meet Good Manufacturing Practice ("GMP") regulations.[29] A Good Clinical Practice ("GCP") audit is also conducted of at least one pivotal study to assure the accuracy of the clinical data.[30] An audit entails one or more visits to clinical trial sites, examination of original patient records or notebooks, and tracking of data from the original clinical trial data forms through the NDA in order to ensure that there are no omissions, mistakes, or misrepresentations. This process ensures that the data are valid and accurate.

One hundred and twenty days after submission of the NDA for review, a drug sponsor must submit a "safety update," which includes any and all additional human use experience and adverse events that may have been observed since the NDA was submitted to the FDA. Additional data submissions may be planned at the time of initial submission

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[28] *See Committees and Meeting Materials*, available at https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/default.htm.

[29] *See* FDA Chapter 46: Compliance Program 7346.832: Pre-Approval Inspections/Investigations, available at https://www.gmp-compliance.org/guidelines/gmp-guideline/fda-chapter-46-compliance-program-7346-832-pre-approval-inspections-investigations.

[30] *See Information Sheet Guidance For IRBs, Clinical Investigators, and Sponsors FDA Inspections of Clinical Investigators*, available at https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm126553.pdf.

and filing (*e.g.*, results of additional long-term follow-up), may represent responses to specific questions or discipline review letters, or may be part of the safety update required under regulations.[31] It is critical to review these data to determine whether safety conclusions are affected, particularly with respect to serious or fatal events.

When all reviews are completed, FDA will transmit either a letter of approval or a "complete response" letter. A complete response is issued when FDA finds deficiencies in the NDA that require correction before the NDA can be approved.

The first complete review sequence and decision by FDA is referred to as the first review cycle.[32] Often, more than one review cycle is undertaken prior to FDA approval.[33] In this case, the sponsor is expected to present new data in the resubmitted NDA that is responsive to the non-approvability issues identified by FDA in the preceding review cycle.

Even where the FDA approves a medicine, it may require additional studies to be done after approval (which is referred to as "post-approval" or "post-marketing").[34] These studies, known as post-approval or postmarketing commitments, may investigate other potential uses or doses of the medicine, or potential safety issues.

The entire NDA review process can take from six months to a year or more, depending upon the complexity and amount of data, and whether the FDA asks the sponsor

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[31] *See* 21 CFR § 314.50(d)(5)(vi)(b); 21 CFR § 314.110.

[32] *See Good Review Management Principles and Practice s for New Drug Applications and Biologics License Applications Guidance for Industry and Review Staff*, available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/good-review-management-principles-and-practices-new-drug-applications-and-biologics-license.

[33] Sacks LV, Shamsuddin HH, Yasinskaya YY et al. Scientific and regulatory reasons for delay and denial of FDA approval of initial applications for new drugs, 2002-2012. JAMA 2014;11(4):378-84, available at https://jamanetwork.com/journals/jama/fullarticle/1817795.

[34] *See Postmarketing Clinical Trials*, available at https://www.fda.gov/vaccines-blood-biologics/biologics-post-market-activities/postmarketing-clinical-trials.

to submit additional information. The extent or level of FDA review is penetrating and detailed.

No other regulatory agency in the world undertakes the level of critical, objective review of NDAs that the FDA applies.

C. The FDA also approves certain medications as safe and effective under abbreviated approval pathways, including via ANDAs.

In contrast to the new drug development and approval processes, certain medications (including generic drugs) enjoy an abbreviated pathway to marketing. Under the Federal Food, Drug and Cosmetic Act (the "FDCA" or the "Act"), there are additional pathways to approval beyond NDAs approved under § 505(b)(1) of the Act, namely those approved under ANDAs and those approved under § 505(b)(2).[35]

ANDAs. There are two types of ANDAs.[36] One, under § 505(j), relies on the FDA's previous determinations of safety and efficacy of previously approved drugs that serve as the basis for ANDAs, which are known as reference listed drugs ("RLDs"). Apart from the technical certifications and data submissions listed above, no separate clinical confirmation of safety and effectiveness is required for an ANDA approval under § 505(j). Rather, the FDA's determination of safety and efficacy of the medication submitted under an ANDA relies on its earlier determination of the same for the RLD on which the ANDA is based. ANDAs are reviewed by scientists in the Divisions of the FDA's Office of Generic Drugs. The FDA's reviews of ANDA can include the following: (a) confirmation

[35] *See* FDA Draft Guidance, *Determining Whether to Submit an ANDA or a 505(b)(2) Application* (October 2017), available at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM579751.pdf.

[36] *See generally* 21 C.F.R. §§ 314, 320; Final Rule, *Abbreviated New Drug Applications and 505(b)(2) Applications*, Fed. Reg. Vol. 81, No. 194 (Oct. 6, 2016), available at https://www.govinfo.gov/content/pkg/FR-2016-10-06/pdf/2016-22690.pdf.

that the proposed indications have been previously approved for safety and efficacy in the RLD; (b) proof that the generic drug active ingredient(s) are identical to that of the RLD; (c) documentation that the route of administration, dosage form and strength are the same as the RLD; (d) data and statistics to show that the drug is bioequivalent to the RLD; (e) labeling that is the same as the RLD; (f) chemistry, manufacturing, and controls data; and (g) certifications of the status of the RLD patents and exclusivity.

The second approval pathway for ANDAs is § 505(j)(2)(C). This is known as a "petitioned ANDA," and it is "for a drug product that differs from the RLD in its dosage form, route of administration, strength, or active ingredient (in a product with more than one active ingredient) and for which FDA has determined, in response to a petition submitted under section 505(j)(2)(C) of the Act (suitability petition), that studies are not necessary to establish the safety and effectiveness of the proposed drug product."[37]

505(b)(2). Another abbreviated pathway for FDA approval of a product that has the same active ingredient in an already approved drug is spelled out in § 505(b)(2) of the Act. A 505(b)(2) application is an NDA that, while it can contain "full reports of investigations of safety and effectiveness," may draw on "studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use."[38] This means that a sponsor submitting a new drug product in a 505(b)(2) application may employ information in its NDA that comes from existing sources, such as published reports.

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[37] *Id.* at 3; 21 U.S.C. § 355(j)(2)(C).

[38] *See* FDA Draft Guidance, *Determining Whether to Submit an ANDA or a 505(b)(2) Application* (October 2017), available at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM579751.pdf, at 2.

V. THE FDA'S REVIEW AND APPROVAL OF KADIAN®

Kadian® is morphine sulfate extended-release in tablet form that is available in several strengths, namely 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 80 mg, 100 mg, and 200 mg.[39]

Kadian® was originally approved by the FDA in 1996, more than two decades ago, and well over a decade before Kadian® was acquired by a former Allergan affiliate in late December 2008. Allergan Sales, LLC currently holds NDA 020616 for Kadian®. Neither Allergan Sales, LLC nor any other current or former affiliates sponsored Kadian®'s original NDA submission. In December 2008, Allergan's then-affiliate (Actavis Elizabeth, LLC) acquired Kadian® from an unaffiliated entity (King Pharmaceuticals, Inc.), which had recently merged with Alpharma, the prior owner of Kadian®.

The IND for Kadian® (which was referred to as Kapanol, then the medication's trade name in other regions)—IND 35553—was opened in 1988.[40] Between 1988 and 1995, there were dozens of interactions between the FDA and the IND holder, including the submission and revision of study protocols, safety reports, reports on the results of studies, and others.[41]

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[39] *See* Kadian Prescribing Information (revised September 2018), available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/020616s061s062lbl.pdf. Kadian® was originally approved in three strengths—20 mg, 50 mg, and 100 mg (*see* Kadian FDA Approval Letter, ALLERGAN_MDL_00798619)—and the additional strengths were subsequently approved by the FDA over time, giving prescribers additional options.

[40] *See, e.g.*, *IND # 35,553-(Kapanol) KADIAN Submission History*, ALLERGAN_MDL_02195542 at ALLERGAN_MDL_02195542.

[41] *Id.* at ALLERGAN_MDL_02195542 to ALLERGAN_MDL_02195548.

On June 28, 1995, Faulding Inc.[42] submitted Kadian®'s New Drug Application to the FDA.[43] The Kadian® NDA and related FDA review documents contain a wealth of information about the clinical studies and other medical information considered by the FDA in approving the medication as safe and effective.[44] The cover letter to the FDA stated that the medication's "clinical development program" was developed in conjunction with the FDA and that the program "consisted of eleven pharmacokinetic studies and six clinical efficacy and safety studies."[45]

Those studies include the following:

- **Two pivotal studies:** CDD-14556 was one of the two pivotal studies (*i.e.*, phase 3 studies intended to provide evidence for approval). The Kadian® NDA described Study CDD-14556 as a "randomized, double-blind, double-dummy parallel group comparison of [Kadian®] q24h, [Kadian®] q12h, and MS Contin®[46] q12h in patients with moderate to severe cancer pain."[47] This study found, *inter alia*, that "[t]here were no statistically significant differences among the groups with respect to quality of sleep or the investigator global assessment, although the trends favored the [Kadian®] groups over MS Contin®" and that "[t]he global assessment in which the patients evaluated their own pain control demonstrated a significantly better rating for [Kadian®] q24h than for MS Contin®." Study MOR-9/92 was the

[42] Faulding later changed its name to Alpharma.
[43] *See* Kadian New Drug Application 020616 (hereinafter "Kadian® Application"), ALLERGAN_MDL_00760226. The original application was for the 20 mg, 50 mg and 100 mg strengths; later strengths were subsequently approved. *Id.* at ALLERGAN_MDL_00760226.
[44] *See generally id.*
[45] *Id.* at ALLERGAN_MDL_00760226.
[46] MS Contin was approved by FDA in 1987. The purpose of employment of MS Contin in the above described efficacy trials of Kadian® was to provide comparison with an active control treatment that FDA had approved as safe and effective.
[47] "q24h" refers to one-daily dosing, and "q12h" refers to once-daily dosing.

other of the two pivotal studies. MOR-9/92 was a "randomized, double-blind, double-dummy, two-period crossover comparison of [Kadian®] capsules q24h with MS Contin® tablets q12h in patients with moderate to severe cancer pain." Among other results and conclusions drawn from this study, the Kadian® Application stated "[a]ll of the efficacy data collected in the present study indicate that, at steady state, the two dosage formulations are statistically and clinically indistinguishable."[48]

- **Supportive controlled trials:** The Kadian® NDA included two additional completed controlled studies.[49] Study MOBES-8/90 was a "randomized, double-blind, double-dummy crossover study comparing the efficacy and safety of [Kadian®] q12h to IRM solution q4h in the management of patients with moderate to severe cancer pain during the two 7 ± day treatment arms of the crossover period." The Kadian® NDA listed several conclusions, including that Kadian "Capsules are efficacious during long-term use." Study MOB-1/90 was a "randomized, open-label, three-way crossover trial comparing the steady-state pharmacokinetics of oral IRM solution q4h, [Kadian®] capsules q12h, and MST Continus® [Australian and European trade name for MS Contin] q12h."[50] Efficacy data from MOB-1/90 indicated "no differences between any of the treatment groups when measured at steady-state on Day 7 of each of the crossover arms."[51]

[48] *Id.* at ALLERGAN_MDL_00760487 to ALLERGAN_MDL_00760502

[49] In addition to these two completed controlled studies, a third controlled study (Study MOR-2/92) was described in the Kadian® Application, but the study was not completed. *Id.* at ALLERGAN_MDL_00760503, ALLERGAN_MDL_00760511. Thus, though "no conclusions related to the study efficacy objectives" could be drawn," "[a]ll safety data" was "fully reported" to the FDA. *Id.*

[50] *Id.* at ALLERGAN_MDL_00760503 to ALLERGAN_MDL_00760514.

[51] *Id.* at ALLERGAN_MDL_00760514.

- **Open-label extension studies:** In addition to those controlled studies, the Kadian® Application described five "open-label extension studies" conducted to study the safety and efficacy of Kadian®. Four of these (Studies MOS-1/91, MOS-2/91, MOS-3/91 and MOR 3/92) originated as extensions of previously completed studies. Study MOS-1/91 was a "single-center, open-label, 12-week efficacy and safety evaluation which followed the open-label, randomized pharmacokinetic crossover study MOB-1/90 described above." Among other conclusions, based on this study, the Kadian® Application states that "[t]he data presented above indicate that from both the patient's and investigator's perspective, pain was acceptably controlled with no loss of pain control with time" and that "patients indicated they had received a generally acceptable level of sleep quality." Based on Studies MOS-2/91 and MOS-3/91, the Kadian® NDA stated: "In conclusion, pain control throughout the 9-month open-label extension period continued to be acceptable with some patients requiring occasional doses of rescue medication." Further, and significantly, in Study MOR-3/92 "[s]even of the eight patients who completed the 9-month studies, MOS-2/91 and MOS-3/91" and who "went on to enroll in the present study which was 12 months in duration." In this study, "[a]ll patients received open-label [Kadian®] capsules every 12 hours." Based on MOR-3/92, the Kadian® NDA concluded that "[Kadian®] capsules given every 12 hours were safe and effective were administered over a period of up to 21 months." Further, MOR-5/92 "was a multicenter, open-label, parallel group study to investigate pain control during transfer from IRM solution or MS Contin® tablets to [Kadian®] capsules and from [Kadian®] capsules to parenteral morphine in patients with moderate to

severe cancer pain." The study's "objective was to investigate if pain control was maintained or if the quality of sleep and the severity of side effects were altered when oral IRM solution q4h or oral MS Contin® q12h controlled-release morphine sulfate tablets were replaced with oral [Kadian®] capsules administered either q12h or q24h for the treatment of moderate to severe chronic pain associated with cancer." On the basis of this study, the Kadian® NDA states, among other things, that "[w]ithin several days of treatment, both [Kadian®] treatments proved to be as efficacious as IRM solution and MS Contin®, and indeed, were preferred by the majority of patients."[52]

On the basis of this clinical program, the Kadian® NDA lists a number of other conclusions, among them the following:[53]

- "In the management of moderate to severe chronic pain, Kadian® administered both every 24 hours and every 12 hours has an efficacy profile clinically and statistically similar to that of MS Contin® q12h and IRM q4h when assessed using established measures of efficacy."
- "In two double-blind, double-dummy controlled clinical trials, Studies MOBES-8/90 and MOR-9/92, there were no differences in the use of rescue medication on the first day of treatment with Kadian® q12h and q24h compared to the last day of treatment with immediate-release morphine q4h or controlled-release MS Contin® q12h. Therefore, patients stabilized to adequate clinical effect with other oral

[52] *Id.* at ALLERGAN_MDL_00760514 to ALLERGAN_MDL_00760533.
[53] *Id.* at ALLERGAN_MDL_00760547.

morphine formulations may be safely transferred to Kadian® at the same total daily morphine dose."

- "During the long-term open-label studies of Kadian® q12h, there was no indication of diminution of analgesia in patients with cancer treated for up to 24 months. Dose escalations that did occur were consistent with disease progression."

The Kadian® clinical program was, in my view, entirely appropriate and state-of-the-art in design, execution, and analysis. The two pivotal trials and one supportive trial were randomized, double-blind, double-dummy comparisons in patients with moderate to severe pain; thus, they directly supported the approved claim of efficacy, and providing safety information under controlled conditions. Safety and risk conclusions from the extensive Kadian® clinical program were consistent with knowledge from decades of clinical experience with a variety of opioid products.

On July 3, 1996, the FDA approved the Kadian® NDA.[54] In its approval letter, the FDA explained that Faulding had demonstrated that Kadian® was safe and effective:

> "We have completed the review of this application, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that ***the drug product is safe and effective*** for use as recommended in the enclosed draft labeling. Accordingly, the application is approved effective on the date of this letter."[55]

[54] Kadian® NDA Approval Letter, ALLERGAN_MDL_00798619.
[55] *Id.* at ALLERGAN_MDL_00798619 (emphasis added).

The FDA's approval letter included draft labeling, which stated that Kadian® was "indicated for the management of moderate to severe pain where treatment with an opioid analgesic is indicated for more than a few days."[56]

Subsequently, Faulding/Alpharma submitted numerous supplements to the NDA and obtained the FDA's approval of a number of additional strengths.[57] By the time of the acquisition of the medication by Allergan's former affiliate in late 2008, not only had Kadian® been on the market and used for an extended period, but FDA had repeatedly reviewed the Kadian® NDA and its labeling, approving a number of labeling revisions based upon information submitted by the prior owner about Kadian®, for more than a decade. As noted above, the Kadian® NDA was transferred from Alpharma Pharmaceuticals, LLC to Actavis Elizabeth, LLC (the former Allergan affiliate) effective December 29, 2008.[58]

VI. THE FDA'S APPROVAL OF NORCO®

Norco® is a combination analgesic product that combines the opioid medication hydrocodone bitartrate with the non-opioid analgesic acetaminophen (a branded example of which is Tylenol). There are three strengths of Norco® currently available; each strength contains 325 mg of acetaminophen, and only the amount of hydrocodone differs. Specifically, those are 5 mg hydrocodone bitartrate/325 mg acetaminophen, 7.5 mg

[56] *Id.* at ALLERGAN_MDL_00798628.

[57] *See, e.g.*, NDA 020616 Supplement History, ALLERGAN_MDL_02202521 at ALLERGAN_MDL_02202521 to ALLERGAN_MDL_02202543 (describing supplements to the NDA between approval and January 2009, when the NDA was transferred to the former Allergan affiliate).

[58] January 8, 2009 Letter to FDA - *Transfer of Ownership of New Drug Application*, ALLERGAN_MDL_02218423.

hydrocodone bitartrate/325 mg of acetaminophen, and 10 mg hydrocodone bitartrate/325 mg acetaminophen.[59]

This medication is sold under the brand name Norco®, but it was approved using the ANDA pathway rather than via the NDA pathway. As set out above, applicants who proceed under ANDAs are not required to independently establish clinical safety and effectiveness; rather, in approving ANDA products as safe and effective, the FDA relies on its previous determination that the RLD on which the ANDA is based is safe and effective. Because the new product must be deemed bioequivalent to the RLD as part of the ANDA process, safety and efficacy testing need not be repeated and instead the FDA can rely on its previous determinations.

Norco® was originally approved by the FDA under two separate ANDAs. *First*, ANDA 40148 was sponsored by Watson Laboratories, Inc. (a former affiliate of Allergan) and was originally submitted, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, on June 7, 1995.[60] The application was for two products, Norco® in its 10 mg/325 mg strength as well as a 10 mg/500 mg strength of generic Hydrocodone Bitartrate and Acetaminophen that has since been discontinued.[61] The FDA approved this ANDA as safe and effective on February 14, 1997.[62] The FDA's approval package for ANDA 040148 states that the FDA had "concluded that these drugs [referring to several strengths of Norco] are ***safe and effective*** for use as recommended the submitted labeling."[63]

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[59] Norco® PI (revised September 2018) at 2, available at https://www.allergan.com/assets/pdf/norco_pi.

[60] *See* FDA Approval Materials for ANDA 40-148, ALLERGAN_MDL_04161199 at ALLERGAN_MDL_04161203.

[61] *Id.*

[62] *Id.*

[63] *Id.* (emphasis added).

Additional strengths were subsequently added under this ANDA number. For example, on September 12, 2000, the FDA approved the 7.5 mg/325 mg strength of Norco®.[64] In its approval letter, the FDA stated that it had "concluded that the new 7.5 mg/325 mg strength of the drug product is safe and effective for use as recommended in the submitted labeling."[65]

Second, the other ANDA under which Norco is currently sold—ANDA 040099—was originally approved on June 25, 1997.[66] This ANDA was not submitted by Allergan or any current or former affiliate. Instead, it was submitted by an unaffiliated company, UCB Pharma, Inc.[67] After approval, Watson acquired this ANDA several years later, in or around 2000.[68] Prior to its acquisition by Watson, UCB marketed it under the trade name Lortab, which was the trade name under which ANDA 040099 was originally approved. After the acquisition, Watson sold the medication approved under this ANDA using the trade name Norco® (as does a current Allergan affiliate). Like the approval letter for ANDA 040148, the approval letter stated that the FDA had "concluded that the drug is safe and effective for use as recommended in the submitted labeling."[69] The strength submitted under this application was 5 mg of hydrocodone bitartrate and 325 mg of acetaminophen.[70]

For both Norco® ANDAs, among the RLDs on which the FDA relied for its safety and efficacy conclusions was Vicodin. The FDA's previous determination with respect to

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[64] *See* FDA Approval Materials for ANDA 40-148/S-002, S-003, S-004, S-005 and S-011, ALLERGAN_MDL_04161243.
[65] *Id.* at ALLERGAN_MDL_04161246.
[66] June 25, 1997 FDA Approval Letter, ALLERGAN_MDL_03280913.
[67] *Id.*
[68] December 13, 1999 Watson Pharmaceuticals, Inc. Board Meeting Minutes, ALLERGAN_MDL_03365064 at -5069 to -5070.
[69] *See* FDA Approval Materials for ANDA 40-148, ALLERGAN_MDL_04161181 at ALLERGAN_MDL_04161184.
[70] *Id.*

the safety and efficacy of Vicodin aided in its determination of safety and efficacy with respect to Norco. The application approval materials for ANDA 040148, for example, stated: "The drug product, Hydrocodone Bitartrate and Acetaminophen Tablets USP, 10 mg/325 mg (Norco) can be expected to have the same therapeutic effect as that of the listed drug product upon which the Agency relied as the basis of safety and effectiveness."[71]

VII. THE FDA'S ONGOING OVERSIGHT

A. The FDA has long regulated and permitted the use of prescription opioids; it continues to approve new prescription opioids.

The FDA has long regulated and monitored prescription opioid pain medications, including their misuse and abuse. In fact, the FDA maintains a webpage, which it regularly updates, setting out in timeline form its many "Activities and Significant Events Addressing Opioid Misuse and Abuse."[72] The FDA's timeline begins in 1911, with most events beginning in the early 2000s and continuing into 2019.[73]

The FDA's actions recognize—and work to mitigate—the risks of addiction, overdose, misuse and abuse.[74] These include, among many others, the Opioid Analgesics Risk Evaluation and Mitigation Strategies ("REMS") (*see infra* § X) and labeling changes (*see infra* § IX). They also demonstrate the FDA's continued recognition of the important role that opioids can play in the proper treatment of pain by physicians and other

[71] ALLERGAN_MDL_04161107 at -1110; *see also* ALLERGAN_MDL_04161181 at -1184 (stating, with respect to ANDA 040099, that the FDA had determined that the medication could "be expected to have the same therapeutic effect as that of the listed drug product upon which the Agency relied as the basis of safety and effectiveness").
[72] *See* FDA Webpage re *Timeline of Selected FDA Activities and Significant Events Addressing Opioid Misuse and Abuse*, available at https://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM566985.pdf (hereinafter "FDA Timeline").
[73] *Id.*
[74] *Id.*

prescribers.[75] For example, the FDA has found that, "[w]hen prescribed and used properly, opioids can effectively manage pain and alleviate suffering—clearly a public health priority."[76] In support of this finding, the FDA has observed that "[c]hronic pain is a serious and growing public health problem: it 'affects millions of Americans; contributes greatly to national rates of morbidity, mortality, and disability; and is rising in prevalence.'"[77] In addition, the FDA has recognized that there is evidence that pain is inadequately treated.[78] The FDA states on its website that, "[a]ccording to the National Institutes of Health, studies have shown that properly managed medical use of opioid analgesic compounds (taken exactly as prescribed) is safe, can manage pain effectively, and rarely causes addiction."[79]

Evidencing that the FDA continues to believe that the benefits of opioids outweigh their risks, the FDA continues to approve New Drug Applications for opioid pain medications, including extended-release formulations and hyper-potent versions. In the last five years, the FDA has approved the following, among others:[80]

- **November 20, 2014:** Hysingla ER, extended-release hydrocodone bitartrate.

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[75] *Id.*

[76] Sept. 10, 2013 Response to PROP Citizen Petition, at 2, available at http://www.supportprop.org/wp-content/uploads/2014/12/FDA_CDER_Response_to_Physicians_for_Responsible_Opioid_Prescribing_Partial_Petition_Approval_and_Denial.pdf (hereinafter "FDA Response to PROP Petition").

[77] *Id*. (quoting Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research, Committee on Advancing Pain Research, Care, and Education; Institute of Medicine, 2011:1-364).

[78] *Id*.

[79] *See* FDA Webpage on *A Guide to Safe Use of Pain Medicine*, available at https://www.fda.gov/consumers/consumer-updates/guide-safe-use-pain-medicine; Lembke Dep. Ex. 21.

[80] *See* FDA Timeline.

- **October 2, 2015:** MorphaBond, extended-release morphine sulfate (like Kadian®).
- **April 26, 2016:** Xtampza ER, extended-release oxycodone.
- **April 20, 2017:** RoxyBond, immediate-release oxycodone hydrochloride.
- **November 2, 2018:** Dsuvia, a sufantenil sublingual tablet, an extremely potent opioid, 10 times stronger than fentanyl, for use in limited circumstances.[81]

The approval process, however, is not the end of the story. If the FDA subsequently determines that the benefits of a medicine do not outweigh the risks, the FDA can request that application holder remove the medicine from the market. The FDA can also withdraw its approval of the medication.[82] Among the reasons that the FDA may withdraw approval are when the FDA finds that "clinical or other experience, tests, or other scientific data show that the drug is unsafe for use under the conditions of use upon the basis of which the application or abbreviated application was approved," that "new evidence of clinical experience, not contained in the application or not available to the FDA until after the application or abbreviated application was approved, or tests by new methods, or tests by methods not deemed reasonably applicable when the application or abbreviated application was approved, evaluated together with the evidence available when the application or abbreviated application was approved, reveal that the drug is not shown to be safe for use under the conditions of use upon the basis of which the application or abbreviated application was approved," "[u]pon the basis of new information before FDA with respect to the drug, evaluated together with the evidence available when the application or

[81] *See* FDA Approval Letter for Dsuvia, available at https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2018/209128Orig1s000Ltr.pdf.
[82] 21 C.F.R. § 314.150 ("Withdrawal of approval of an application or abbreviated application.").

abbreviated application was approved, that there is a lack of substantial evidence from adequate and well-controlled investigations as defined in 314.126, that the drug will have the effect it is purported or represented to have under the conditions of use prescribed, recommended, or suggested in its labeling," or "[t]hat the application or abbreviated application contains any untrue statements of a material fact."[83]

B. The FDA has imposed Postmarketing Requirements to further study and monitor the risks and benefits of prescription opioids.

In 2007, Congress amended the Federal Food, Drug, and Cosmetic Act, giving the FDA power to require postmarketing requirements ("PMRs").[84] Specifically, the FDA was given the power to "require … a postapproval study or studies of the drug, or a postapproval clinical trial or trials of the drug."[85] Postapproval studies or clinical trials are authorized where the FDA becomes aware of "new safety information," defined as "a serious risk or an unexpected serious risk associated with use of the drug that the [FDA] has become aware of … since the drug was approved, since the risk evaluation and mitigation strategy was required, or since the last assessment of the approved risk evaluation and mitigation strategy for the drug," or "the effectiveness of the approved risk evaluation and mitigation strategy for the drug obtained since the last assessment of such strategy."[86]

The purpose of a postapproval study or clinical trial is (i) "[t]o assess a known serious risk related to the use of the drug involved"; (ii) "[t]o assess signals of serious risk related to the use of the drug"; and (iii) "[t]o identify an unexpected serious risk when available data indicates the potential for a serious risk."[87] To meet these goals, the FDA

[83] *Id.* at § 314.150(a)(2).
[84] 21 U.S.C. 355(o).
[85] 21 U.S.C. 355(o)(3)(A).
[86] 21 U.S.C. § 355-1(b)(3); *see* 21 U.S.C. § 355(o)(3)(C).
[87] 21 U.S.C. § 355(o)(3)(B).

must first require a postapproval study; only if the FDA concludes that a study would not be sufficient to meet these goals may the FDA require a postapproval clinical trial.[88]

As explained below, in its September 10, 2013 response to a Citizen Petition filed by a group called the Physicians for Responsible Opioid Prescribing ("PROP") (*see infra* § VII.C), the FDA stated that, pursuant to its enhanced authority under the Federal Food, Drug, and Cosmetic Act, it was requiring NDA sponsors of extended-release, long-acting opioids to conduct PMRs "to assess certain known serious risks of ER/LA opioid use: misuse, abuse, hyperalgesia, addiction, overdose, and death."[89]

That same day, the FDA sent a letter to Watson Laboratories, Inc. (the former Allergan affiliate that held the Kadian® NDA at the time) notifying the company that the FDA would be requiring PMRs, based in part on the PROP Petition. Specifically, the FDA stated that it "has concluded that more data are needed regarding the serious risks of misuse, abuse, hyperalgesia, addiction, overdose, and death associated with the long-term use of [extended-release long-acting] opioid analgesics."[90] The FDA's letter contained a list of five PMRs, including studies to provide quantitative estimates of the serious risks of opioids associated with long-term use, studies designed to define and validate "doctor/pharmacy shopping" as outcomes of misuse, abuse, or addition, and a clinical trial to estimate the risk of developing hyperalgesia following use of long-acting opioids.[91] In response, Actavis and several other opioid manufacturers entered into an agreement "to

[88] 21 U.S.C. § 355(o)(3)(D)(ii).
[89] FDA Response to PROP Petition at 1-2.
[90] ALLERGAN_MDL_01291325.
[91] *Id*.

effectuate their collaboration to complete the PMRs."[92] The agreement's signatories are known as the Opioid PMR Consortium ("OPC").[93]

A few months later, in April 2014, the FDA announced a public stakeholder meeting to gain insight into the design and conduct of the PMRs.[94] The FDA sought insight on these issues from stakeholders, including patients, academics, researchers, government regulators, healthcare organizations, the pharmaceutical industry, and the general public.[95] Subsequently, the FDA withdrew the original five PMRs and replaced them with eleven PMRs, namely ten studies and one clinical trial.[96]

Several of the PMRs, including the clinical trial, remained ongoing as of May 2019. These studies and trial as well as others of their type are another tool in the FDA's toolbox for its continuing oversight and regulation of these medications, including their risks.

C. **The FDA has considered a number of opioid-related Citizen Petitions.**

Responses to Citizen Petitions are another way in which the FDA has regulated and overseen prescription opioid medications. A Citizen Petition is a formal mechanism whereby concerned citizens or organizations can provide views, data on a medicine's safety or other relate matter, along with recommendations for FDA actions.

Federal regulations provide for the format, content and submission of Citizen Petitions.[97] FDA regulations, policies, pending or past decisions are all candidate subjects for public critique, comment, and request for modification via the Citizen Petition rules

[92] ALLERGAN_MDL_02342317.
[93] *Id*.
[94] *See Public Meeting; Request for Comments - Postmarketing Requirements for the Class-Wide Extended-Release/Long-Acting Opioid Analgesics*, available at https://www.regulations.gov/document?D=FDA-2014-N-0374-0001.
[95] *Id*.
[96] ALLERGAN_MDL_02023773.
[97] 21 C.F.R. § 10.3.

and procedures. Citizen Petitions and FDA's responses are open to the public and are maintained in an electronically accessible docket. FDA is required to carefully review and respond to each Citizen Petition within 180 days of receiving it. FDA responses to Citizen Petitions reveal FDA's view on the issues raised by each Petition.

There have been a number of Citizen Petitions relating to opioid pain medications. Notably, Physicians for Responsible Opioid Prescribing ("PROP")—an organization led by one of Plaintiffs' disclosed experts (who I understand was subsequently withdrawn by Plaintiffs), Dr. Jane Ballantyne, and which includes on its Board of Directors another proffered expert, Dr. Anna Lembke—submitted a three-page Citizen Petition on July 26, 2012.[98] The Petition outlined several of the group's concerns:

> (a) "[T]he FDA-approved indication for nearly all instant-release opioid analgesics is "moderate to severe pain." For extended-release opioids, the indication is for "moderate to severe pain when a continuous, around-the clock analgesic is needed for an extended period of time."
>
> (b) "These overly broad indications imply a determination by FDA that they are safe and effective for long-term use."
>
> (c) "[A]n increasing body of medical literature suggests that long-term use of opioids may be neither safe nor effective for many patients, especially when prescribed in high doses."

On the basis of these stated concerns, the PROP Citizen Petition requested FDA to modify the current labels of opioid analgesics as follows:

[98] *See* July 25, 2012 PROP Citizen Petition, available at https://www.citizen.org/sites/default/files/2048.pdf (hereinafter "PROP Petition").

1. "Strike the term 'moderate' from the indication for non-cancer pain.""

2. "Add a maximum daily dose, equivalent to 100 milligrams of morphine for non-cancer pain."

3. "Add a maximum duration of 90-days for continuous (daily) use for non-cancer pain."

After receiving the petition, the FDA solicited information and comment from the public. In response to the PROP Citizen Petition, the FDA received over 1,900 comments.[99] Some public health agencies and organizations supported the Petition due to concerns over increased opioid abuse; however, most commenters opposed PROP's requests, including the American Medical Association, the American Society of Anesthesiologists, and several patient advocacy groups. Those in opposition expressed concern that the labeling changes recommended were not supported by scientific evidence, and the proposed uniform approach to maximum dosage and duration of treatment was inconsistent with the need for individualized treatment and the variability among patient responses to opioids.[100]

After receiving these comments, the FDA responded in detail to the PROP Citizen Petition on September 10, 2013, denying the Petition in large part.[101] Despite PROP's requests, the FDA declined to take, among others, several actions. *First*, while PROP had requested a maximum daily dose of the equivalent of 100 milligrams of morphine, the FDA specifically declined to "specify or recommend a maximum daily dose or duration of use

[99] FDA Response to PROP Petition at 5
[100] *Id*.
[101] Id.

for any opioid."[102] In so determining, the FDA found that Dr. Lembke's PROP group's cited "scientific literature does not support establishing a maximum recommended daily dose of 100 mg MED," rejecting PROP's contention that it did.[103] For example, the FDA stated that while "the available data do suggest a relationship between increasing opioid dose and risk of certain adverse events," "the available information does not demonstrate that the relationship is necessarily a causal one."[104] Thus, although PROP had "selected a 90-day limit," PROP had "provide[d] no evidence that addiction (however it is defined) increases significantly after 90 days of use such that it would support a labeling change."[105]

Second, the FDA rejected Dr. Lembke's group's request that the FDA "[a]dd a maximum duration of 90 days for continuous (daily) use."[106] As support for this contention, PROP had argued that "[l]ong-term safety and effectiveness of managing [pain] with opioids has not been established."[107] But the FDA said that PROP's request was "not supportable."[108] In so concluding, the FDA examined the materials cited by Dr. Lembke's group and found them lacking. Critically, the FDA stated that "[t]he cited literature does not identify a duration threshold beyond which the risk of addiction outweighs the benefits of opioid treatment."[109]

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[102] *Id.* at 11-14.
[103] *Id.* at 12.
[104] *Id.* at 16
[105] *Id.*
[106] *Id.* at 14 (internal quotations omitted).
[107] *Id.* (internal quotations omitted).
[108] *Id.*
[109] *Id.* at 16.

Third, the FDA also rejected PROP's proposed distinction for use in opioid labeling between chronic cancer pain, on the one hand, and chronic non-cancer pain, on the other.[110] Specifically, the FDA wrote:

> "All of PROP's labeling change requests are limited to 'non-cancer' pain, a distinction that is not made in current ER/LA opioid analgesic labeling. It is FDA's view that a patient without cancer, like a patient with cancer, may suffer from chronic pain, and PROP has not provided scientific support for why labeling should recommend different treatment for such patients. In addition, FDA knows of no physiological or pharmacological basis upon which to differentiate the treatment of chronic pain in a cancer setting or patient from the treatment of chronic pain in the absence of cancer, and comments to the Petition docket reflect similar concerns. FDA therefore declines to make a distinction between cancer and non-cancer chronic pain in opioid labeling."[111]

In the response, the FDA required some labeling changes, though not to the extent advocated by PROP. For example, the FDA granted the request to remove the term "moderate" from the indication for extended-release, long-acting opioid pain medications.[112] In place of that term, the FDA required applicants to use the following language: "[Name of medication] is indicated for the management of pain severe enough

[110] *Id.* at 9.
[111] *Id.*
[112] *Id.* at 9.

to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate."[113] Likewise, the FDA required additional labeling language "urg[ing] prescribers to weigh carefully whether the benefits of an ER/LA opioid outweigh its serious risks on a patient-by-patient basis."[114] This shows the FDA's recognition of the importance of doctors and other prescribers making decisions about whether to use opioid medications in each individual patient's unique circumstances.

The FDA's responses to Citizen Petitions like PROP's can be useful in revealing the FDA's current thinking about disputed issues regarding drug safety and efficacy. In this case, the FDA's response demonstrated that it stood by its previous determinations on the safety of opioids. It also shows that the FDA rejected several of the core contentions of Plaintiffs and their experts, such as their proposed treatment for chronic non-cancer pain, their proposed restriction on the duration of treatment, and their proposed restriction on the daily dosage.[115]

Another similar example is the FDA's response to a July 20, 2017 Citizen Petition by a group called Pharmaceutical Manufacturing Research Services, Inc ("PMRS").[116]

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[113] *Id.* at 8 (also requiring additional language in "Limitations of Use" section).

[114] *Id.*

[115] In August 2017, PROP submitted another Citizen Petition to the FDA. *See* August 2017 PROP Citizen Petition, Docket No. FDA-2017-P-5396. PROP requested that the FDA remove "ultra-high dosage unit" opioids, arguing that their risks "outweigh their benefits" and that they "should be immediately removed from the market to prevent further harm." *Id.* at 1, 5. On February 28, 2018, FDA responded to PROP's Citizen Petition. *See* February 28, 2018 FDA Response, Docket No. FDA-2017-P-5396. Again, the FDA declined to take immediate action, stating instead that the FDA had "not yet resolved the issues raised in your citizen petition." *Id.* The FDA's refusal to "immediately" remove "ultra-high dosage opioids" from the market indicates that it did not believe that, based on the current science, those medications were not safe and effective.

[116] July 20, 2017 PMRS Citizen Petition, available at https://www.regulations.gov/document?D=FDA-2017-P-4352-0001; FDA Response to July 20, 2017 PMRS Citizen Petition, available at https://www.regulations.gov/document?D=FDA-2017-P-4352-0017.

The PMRS group requested, among other things, that the FDA "[r]efrain from approving all other pending or future applications for opioids indicated for chronic use, including use over 'an extended period of time,' use for 'long-term opioid treatment,' or any other labeling for chronic use."[117] PMRS "contend[ed] that these indications are false and misleading and lack substantial evidence."[118] The FDA considered PMRS's position and "agree[d] that opioid addiction and the resulting overdoses and deaths have created a national crisis," and it "note[d] that the Agency is taking a variety of steps to address this public health concern."[119] Nonetheless, the FDA denied the Petition, stating that it "believe[d] it would be premature to make a determination at this time regarding [PMRS's] specific requests."[120] In denying the Petition, the FDA referred to the ongoing opioid PMRs. *See supra* § VII.B. It stated that, given those pending PMRs, the FDA was "denying [PMRS's] request to take the specified actions at this time insofar as we are continuing to consider, both in the context of application-specific reviews and ongoing PMRs, the issues you raised."[121]

PMRS filed another Citizen Petition in July 2018, to which the FDA responded in December 2018.[122] This Petition asked, among other things, that the FDA stop approving opioid medications with indications for chronic non-cancer pain.[123] Again, the FDA rejected the request of PMRS.[124]

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[117] *Id.*
[118] *Id.*
[119] *Id.*
[120] *Id.*
[121] *Id.* at 4.
[122] *See* December 20, 2018 Response to July 23, 2018 PMRS Petition, Docket No. FDA-2018-P-2851.
[123] *Id.*
[124] *Id.*

As with the PROP Petitions, the FDA's response to these Petitions reflects the Agency's views on these important issues. Its response to the PMRS Petitions, like its response to the PROP Petitions, demonstrates that the FDA does not believe there is sufficient evidence based on the current available research and information to take the steps advocated by PROP or PMRS—which mirror the views of Plaintiffs and their experts here. The FDA's views could change based on later research or information, but this response shows the FDA's current views on these issues based on the science and medical research available at the time. Further, the FDA's receipt of and responses to Citizen Petitions is another example of the ongoing FDA's monitoring and regulation of opioid pain medications.[125]

D. The FDA continually monitors reported adverse events.

As noted earlier in this report, even after a medication is approved, the FDA continues to review the safety of the medication. This continued surveillance includes the review of "adverse drug experience(s)"—often referred to as "adverse events"—that are submitted to the FDA by various sources. Physicians, other healthcare providers, and even patients are encouraged to report suspected adverse events to the manufacturer or directly to the FDA, which then reviews them as part of its ongoing post-approval surveillance. The FDA conducts this surveillance, in part, because not all information regarding the

[125] The National Center for Addiction and Substance Abuse of Columbia University ("CASA")—a group on whose Board of Directors Plaintiffs' proffered expert Dr. Kessler served at the time—also submitted two opioid-related Citizen Petitions, one in October 2007 and another in May 2009. *See* October 25, 2007 CASA Citizen Petition, Docket No. FDA-2007-P-0009; May 15, 2009 CASA Citizen Petition, Docket No. FDA-2009-P-0227. In a June 2013 response, the FDA denied both of CASA's Petitions. *See* June 17, 2013 FDA Response, Docket Nos. FDA-2007-P-0009.

safety and effectiveness of a medication is necessarily known at the time of the FDA's initial approval.[126]

Under 21 C.F.R. § 314.80(b), the holders of each approved NDA and ANDA (among others) must make several types of submissions to the FDA regarding potential adverse events involving their medications. For one, applicants "must report each adverse drug experience that is both serious and unexpected, whether foreign or domestic, as soon as possible but no later than 15 calendar days from initial receipt of the information by the applicant."[127] These are often called 15-day reports. In addition, applicants must submit reports of other adverse drug experiences—*i.e.*, those not reported as 15-day reports—quarterly for the first three years after the application is approved and then annually after that.[128] These are commonly known as periodic reports. With respect to both Kadian® and Norco®, Allergan's current and former affiliates have regularly submitted both 15-day reports and periodic reports, as appropriate.

Such real-world information is valuable to the FDA's post-approval surveillance.[129] As this new information becomes available to the FDA, it "reviews the data and evaluates

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[126] *See, e.g.*, FDA Draft Guidance, *Drug Safety Information — FDA's Communication to the Public*, available at https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm295217.pdf, at 3 ("After drug approval, FDA may learn of new, or more serious or more frequent, adverse drug reactions from, for example, postapproval voluntary or mandatory reporting of adverse drug reactions during use of the drug . . .").

[127] 21 C.F.R. § 314.80(c)(1)(i).

[128] *Id.* at § 314.80(c)(2).

[129] Adverse events, though, are not useful in assessing causation. While adverse event reporting is useful to generate hypotheses, for example, they often lack altogether or even incorrectly report key information or are otherwise unreliable for this purpose. The FDA has been quite clear about the limitations of adverse event reporting in determining causation. For example, the FDA's website states that "there is no certainty that the reported event (adverse event or medication error) was due to the product"; further, "FDA does not require a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event." *See Questions and Answers on FDA's Adverse Event Reporting System (FAERS)*, available at

whether there is an emerging drug safety concern."[130] If there is such a concern, "relevant medical and scientific experts within FDA engage in a prompt review and analysis of available data."[131]

As part of this process, the FDA maintains a database known as the FDA Adverse Event Reporting System ("FAERS") that contains adverse event reports that were submitted to the FDA.[132] The FDA describes FAERS as "a useful tool for FDA for activities such as looking for new safety concerns that might be related to a marketed product."[133] Reports contained in FAERS are evaluated by clinical reviewers at the FDA—namely those in the Center for Drug Evaluation and Research as well as the Center for Biologics Evaluation and Research—"to monitor the safety of products after they are approved by FDA."[134] If the FDA identifies a potential safety concern in FAERS, it conducts further evaluation.[135]

From there, the FDA can take additional regulatory action as appropriate. For example, the FDA might require an update to a product's labeling, restrict the use of a

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https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/surveillance/adversedrugeffects/default.Htm. Nor can one draw any conclusions from the number, frequency or incidence of adverse event reports: "Many factors can influence whether an event will be reported, such as the time a product has been marketed and publicity about an event. There are also duplicate reports where the same report was submitted by a consumer and by the sponsor. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population." *Id.*

[130] *See, e.g.*, FDA Draft Guidance, *Drug Safety Information — FDA's Communication to the Public* at , available at https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm295217.pdf, at 3.

[131] *Id.*

[132] *See Questions and Answers on FDA's Adverse Event Reporting System (FAERS)*, available at https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/surveillance/adversedrugeffects/default.Htm.

[133] *Id.*

[134] *Id.*

[135] *Id.*

medication, communicate safety information to the publication—or even remove a product from the market altogether.[136] For instance, with respect to opioid pain medications specifically, in March 2016 the FDA required a change to the labeling of certain opioid medications—including Kadian®—based in part on FAERS.[137] Specifically, in requiring the disclosure of additional risk information about the "occurrence of adrenal insufficiency in patients following the initiation of an opioid," the FDA wrote that "we have become aware of cases submitted to the FDA's Adverse Event Reporting System (FAERS) similar to those described in the published literature."[138] In that instance, the labels for Kadian® and other opioid medications were revised to provide prescribers additional information on this risk. *See infra* § IX.

At bottom, the reporting and analysis of adverse event information is a crucial tool in the FDA's ongoing surveillance of opioid pain medications, including Kadian® and Norco®.

VIII. FDA WARNING LETTERS

A. Generally

An FDA warning letter is a correspondence that the FDA sends to a regulated entity to notify it of potential violations so that the entity has "an opportunity to take voluntary and prompt corrective action."[139] Warning letters are "informal and advisory."[140]

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[136] *Id.*

[137] *See* March 22, 2016 FDA Letter, ALLERGAN_MDL_02195310.

[138] *Id.* at ALLERGAN_MDL_02195311; *see also id.* at ALLERGAN_MDL_02195310 (also referring to the FDA's search of FAERS to identify cases regarding the "occurrence of serotonin syndrome following the initiation of an opioid in patients who had previously been taking one or more serotonergic drugs").

[139] FDA Regulatory Procedures Manual, § 4-4-1, *available at* https://www.fda.gov/downloads/ICECI/ComplianceManuals/RegulatoryProceduresManual/UCM074330.pdf.

[140] *Id.*

Importantly, a warning letter is not a conclusive determination of wrongdoing; it does not establish liability, and it does not commit FDA to taking enforcement action.

Notably, the FDA is not required to send a warning letter before taking action.[141] If a potential violation is considered serious enough, the FDA will typically take immediate enforcement action, instead of issuing a warning letter.[142] In deciding whether to take enforcement action or to issue a warning letter first, the FDA considers several factors, including the manufacturer's compliance history, the nature of the violation, the risks associated with the violations concerning the product, and whether the FDA reasonably expects that the manufacturer will take prompt corrective action.[143] When the FDA believes that a less serious matter can be resolved informally through voluntary compliance, it will issue a warning letter.[144]

A manufacturer need not accept the FDA's statements in a warning letter. The recipient may challenge or disagree with the FDA's assertions. That a manufacturer opts to comply with the FDA's requests in a warning letter, however, does not mean that the recipient necessarily agrees with the FDA's assertions; rather, the recipient may decide, despite disagreeing with the FDA, that complying with the FDA's requested action is the most appropriate and conservative approach.

Warning letters are issued frequently. Indeed, the FDA issues hundreds of warning letters each year. In 2010 alone—the year that the FDA issued the warning letter regarding

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[141] FDA Regulatory Procedures Manual, § 4-4-1, *available at* https://www.fda.gov/downloads/ICECI/ComplianceManuals/RegulatoryProceduresManual/UCM074330.pdf.

[142] *Id.*

[143] *Id.*

[144] *Id.* at 42 (noting that a warning letter is the FDA's "principal means of achieving prompt *voluntary* compliance with the Federal Food, Drug, and Cosmetic Act.") (emphasis added).

Kadian® marketing to an Actavis entity—the FDA issued more than 600 warning letters.[145] Thus, although warning letters must be taken seriously, they are common and do not alone demonstrate that any wrongdoing has occurred.

In addition to warning letters, the FDA has many options for actions it may decide to take. It does, in fact, commonly take such actions. For example, the following chart from the FDA's website illustrates the number of certain types of actions taken in Fiscal Year 2017:[146]

FDA Enforcement Statistics
Summary
Fiscal Year 2017

Enforcement Type	Count
Seizures	3
Injunctions	12
Warning Letters	15318
Recall Events	2945
Recalled Products	9199
Drug Product Debarments	5
Food Importation Debarments	0

In sum, a warning letter is an "informal and advisory" means by which the FDA may seek to commit a pharmaceutical manufacturer to take voluntary action to self-correct a potential violation.[147]

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[145] *See* http://wayback.archive-it.org/7993/20170112194132/http:/www.fda.gov/ICECI/EnforcementActions/WarningLetters/2010/default.htm?Page=1.

[146] https://www.fda.gov/media/110196/download

[147] FDA Regulatory Procedures Manual, § 4-1-1, *available at* https://www.fda.gov/downloads/ICECI/ComplianceManuals/RegulatoryProceduresManual/UCM074330.pdf

B. **February 2010 Warning Letter Related to Kadian® Promotion**

On February 18, 2010, Actavis (which then held the Kadian® NDA) received a warning letter from the FDA regarding the promotion of Kadian®.[148] In the letter, the FDA identified concerns about two Kadian® promotional pieces, the "Co-Pay Assistance Program brochure" and the "PK to PK Comparison Detailer.[149] The FDA "request[ed]" that Actavis cease distributing these materials and "submit a written response . . . stating whether you intend to comply with this request."[150]

Critically, both the Co-Pay Assistance Program brochure and the PK to PK Comparison Detailer had been submitted to the FDA for its review.[151] These submissions were made under an FDA form, Form 2253. The Form 2253 submissions for both of these materials were made to the FDA months ahead of time. Specifically, Actavis submitted the Co-Pay Brochure on February 16, 2009—more than a year before the warning letter.[152] Actavis submitted the Comparison Detailer on June 24, 2009—more than seven months before the warning letter.[153] Alpharma (Kadian®'s prior owner) had also submitted

[148] ALLERGAN_MDL_00795835
[149] *Id.* at -36.
[150] *Id.* at -45.
[151] 21 C.F.R. § 314.81(b)(3)(i) ("The applicant shall submit specimens of mailing pieces and any other labeling or advertising devised for promotion of the drug product at the time of initial dissemination of the labeling and at the time of initial publication of the advertisement for a prescription drug product.").
[152] *See* ALLERGAN_MDL_01875871 at -873; ALLERGAN_MDL_01777325 (letter to FDA re Co-Pay Brochure, including Form 2253 itself).
[153] *See* ALLERGAN_MDL_01875871 at -873; ALLERGAN_MDL_01290412 (letter to FDA re PK to PK Comparison Detailer, including Form 2253 itself); ALLERGAN_MDL_00445306 (email reflecting submission of Comparison Detailer). Other materials that Allergan's former affiliate identified to the FDA as having similar content as the Co-Pay Assistance Program brochure and the PK to PK Comparison Detailer were likewise submitted by Actavis to FDA under Form 2253, all in November 2009 or earlier. *See, e.g.*, ALLERGAN_MDL_01875871 at -873; ALLERGAN_MDL_01203187 (email reflecting submission of Kadian® "When You Can Prescribe Benefits" material).

versions of both pieces to the FDA even earlier (at least as early as 2008).[154] That means the materials had been submitted to the FDA for review not once but twice, including at least as early as a year and a quarter before the warning letter.

The FDA's letter discussed four potential issues with these materials: (i) "Omission and Minimization of Risk Information"; (ii) "Broadening of Indication/Failure to State Full Indication"; (iii) "Unsubstantiated Superiority Claims"; and (iv) "Unsubstantiated Effectiveness Claims."[155] I describe each below.

"Omission and Minimization of Risk Information": The FDA acknowledged that both the Co-Pay Assistance Program brochure and the Comparison Detailer included "information from the boxed warning and some [of the] adverse reactions associated with Kadian."[156] The FDA also included in both pieces, in bold and italics, the statement: "***Please see accompanying complete Prescribing Information***"—a reference to the FDA approved label, which included a number of risk disclosures and warnings (*see infra* § IX).[157] Nonetheless, the FDA expressed concerns that these materials did not adequately present other risk information.[158] The FDA's concerns appeared to center on whether the risks were presented with the same prominence and clarity as the benefits; the FDA did not suggest that the risks were being completely omitted from the pieces.[159]

"Broadening of Indication and Failure to State Full Indication": The FDA also expressed concerns that the Co-Pay Assistance Program brochure and the Comparison

[154] FDA Warning Letter, ALLERGAN_MDL_00795835 (indicating that the Comparison Detailer had been submitted under Form 2253 by Alpharma); March 10, 2008 Form 2253 submission by Alpharma for "Co-Pay Assistance Program Booklet," ALLERGAN_MDL_02489054.
[155] *See generally* FDA Warning Letter, ALLERGAN_MDL_00795835
[156] *Id.* at -38.
[157] *Id.* at -839.
[158] *Id.* at -838 to -839.
[159] *Id.*

Detailer "suggest[]" and "imply[]" that Kadian® was appropriate for a "broader range of patients than has been demonstrated by substantial evidence or substantial clinical experience."[160]

"Unsubstantiated Superiority Claims": The FDA took issue with several statements in the promotional materials comparing Kadian® to several other morphine-based products, including MS Contin, generic controlled release morphine and Avinza.[161] These concerns relate not to whether opioids are safe or effective, but rather how Kadian® compares to other opioid medications.[162]

"Unsubstantiated Effectiveness Claims": The FDA's last area of concern regarded statements not about the safety of Kadian® but rather its effectiveness.[163] For example, the letter stated that the FDA was "not aware of any studies demonstrating that the level of pain reduction experienced by patients on Kadian therapy corresponds with a positive impact on the outcomes claimed."[164] The FDA asked that Actavis submit any data it had in support of these claims.[165]

I have evaluated the FDA's letter from a regulatory perspective and offer several observations.

First, it is noteworthy that the FDA did not identify any information that was necessarily alleged to be false or true, but rather the FDA was concerned with the completeness and balance of the information presented. Indeed, the letter uses phrases like

[160] *Id.* at -839 to -840.
[161] *Id.* at -841 to -84
[162] *Id.*
[163] *Id.* at -844 to -845.
[164] *Id.* at -845.
[165] *Id.* at -845.

"the ***totality*** of these presentations," "[t]hese presentations in the Comparison Detailer ***suggest***" and "therefore ***implying*** that."[166]

Second, with respect to the presentation of risk information, the FDA expresses concerns not that the materials fail to present warnings about addictiveness and other risks altogether but rather that, for example, the materials "fail[ed] to ***present risk information with a prominence and readability*** that is reasonably comparable to the presentation of benefit information."[167]

Third, the letter makes clear that the statements in the promotional materials were supported by citations to scientific research and evidence. The FDA does not claim that there is a dearth of such support but rather that the FDA's interpretation of that medical information differs from that implied by the materials. For example, the letter acknowledges that the Comparison Detailer cited to a published article—the "Gourlay et al. article, which describes one of the pharmacokinetic studies presented in the PI (Study# MOR-9/92)"—in support of statements regarding comparisons to MS Contin.[168] The FDA's quarrel was that the "pharmacokinetic differences between Kadian and MS Contin" reported in the Gourlay article did not necessarily support the conclusion that there were "any clinical consequences" of those differences.[169] Put differently, the FDA's letter is concerned primarily not with whether there is clinical research regarding Kadian® on various points but rather how to interpret that support.

[166] *Id.* at -839 to -840 (emphasis added).
[167] *Id.* at -838 to -839 (emphasis added).
[168] *Id.* at -842.
[169] *Id.* at -842.

Fourth, both of the materials in question had been submitted by both Alpharma (in materially similar form) and Actavis Elizabeth, LLC under Form 2253. That the FDA raised its concerns in a warning letter and that Actavis Elizabeth, LLC took promotion action illustrates the FDA's process for review of promotional materials working as intended and underscores the FDA's extensive oversight over the industry. *See*, *e.g.*, *infra* § XI.B.

Fifth, and in any case, the FDA did not conclusively determine that Actavis did anything wrong. As explained above, a warning letter simply communicates the FDA's position on a matter; it does not establish liability or commit to the FDA to taking enforcement action. The letter repeatedly gives Actavis the option to submit additional information to further support the statements in the promotional materials, stating, for example, "[i]f you have data to support these claims, please submit the data to FDA for review." Nor does the FDA state that it would take enforcement or other additional action against Actavis. Instead, the letter concludes by asking for a written response from Actavis and inviting the submission of a "comprehensive plan of action to disseminate truthful, non-misleading, and complete corrective messages about the issues discussed in this letter to the audience(s) that received the violative promotional materials." As set out below, Actavis accepted the invitation.

In sum, not only does the FDA warning letter not establish any wrongdoing on Actavis's behalf, but to the extent the marketing with which it was concerned could have led to any misimpressions in any prescribers at all, Actavis quickly provided corrective information that would have promptly dispelled them, as described below.

C. The response to the warning letter was prompt and comprehensive.

After receiving the warning letter, Actavis had a number of options. Most notably, it could have contested the FDA's allegations or rebutted the FDA's allegations with additional clinical research studies or data. Actavis, however, chose the most conservative course, deciding to work with the FDA voluntarily to address the FDA's concerns outlined in the warning letter. In so doing, Actavis was not required to and in fact did not agree that the statements in its marketing materials were false or misleading.[170] Still, it took the most responsible, conservative approach to the FDA's concerns.

The day after receiving the warning letter, Allergan's former affiliate instructed the small contract salesforce who was then detailing[171] Kadian® to "immediately cease distributing the Co-Pay Assistance Program Brochure and Comparison Detailer," and to remove these pieces from physicians' offices where they could.[172] In addition, it told its salesforce that there may be other Kadian® promotional materials containing messages similar to those at issue in the warning letter; thus, all promotional pieces were to be quarantined until further notice.[173] Actavis also reminded the salesforce to restrict all communications with healthcare professionals to the information contained in the Kadian® label.[174]

Next, in accordance with the FDA's instructions, Actavis submitted a response to the FDA on March 4, 2010.[175] In that response, Actavis stated that it had reviewed all of

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[170] *See, e.g.*, N. Leitch Dep. Tr. at 198:11-20; J. Altier Dep. Tr. at 88:9-15.
[171] Detailing commonly refers to the practice of pharmaceutical sales representatives visiting physicians to provide them with information regarding a medication.
[172] ALLERGAN_MDL_01869507.
[173] *Id.* at -07–08.
[174] *Id.* at -08.
[175] ALLERGAN_MDL_01396751.

its promotional materials currently in use and had determined that each contained claims within the scope of the warning letter.[176] Actavis informed the FDA that it instructed its sales force to cease using all promotional materials, and to return the Co-Pay Assistance Program brochure and Comparison Detailer for destruction.[177] Actavis listed the promotional materials in circulation in Attachment C and included information indicating when those materials were initially submitted to the FDA for review.[178] Actavis also committed to addressing the issues raised in the warning letter in all Kadian® promotional materials going forward.[179] In addition, Actavis proposed disseminating "Dear Healthcare Professional" and "Dear Consumer" letters to those who received the implicated materials, and included proposed versions of those letters in Attachments A and B, respectively.[180] Specifically, the "Dear Healthcare Professional" letter would be sent to all physicians who might have received the Comparison Detailer.[181] The "Dear Consumer" letter would be sent to any individuals who received Co-Pay materials directly from Actavis. To reach those consumers who might have used the Co-Pay materials after obtaining them from physicians' offices, Actavis offered to distribute "Dear Consumer" letters to those offices and request that the physicians place the letters in their office waiting rooms.[182] Finally, Actavis committed to retraining its salesforce and revising its Standard Operating

[176] *Id*.
[177] *Id*. at -52; *see* March 9, 2010 T. Nataline Email, ALLERGAN_MDL_01436179 (instructing salesforce to return all Kadian promotional pieces for destruction).
[178] ALLERGAN_MDL_01396751 at -69.
[179] *Id*. at -52.
[180] *Id*. at -52–53.
[181] *Id*.
[182] *Id*. at -53.

Procedure for reviewing and approving promotional labeling and advertising to "provide a more rigorous and balance review of materials."[183]

The FDA responded on March 26, 2010.[184] Regarding Actavis's corrective-action plan, the FDA explained that it "appreciate[d] the steps that Actavis has taken thus far to address the issues outlined in the Warning Letter," and that it has "reviewed [Actavis's] corrective action plan and ha[s] no further comments at this time."[185] Regarding Actavis's proposed dissemination plan, the FDA requested confirmation that the "Dear Healthcare Professional" letter be sent to "all physicians that could have been exposed to the Comparison Detailer."[186] In addition, the FDA requested clarification whether Actavis could personally contact patients who redeemed the Co-Pay materials to ensure that they receive "Dear Consumer" letters; and the FDA agreed with Actavis's recommendation to distribute "Dear Consumer" letters to physician offices, but recommended that those letters be included in a display stand to draw consumers' attention to the letters.[187] The FDA also offered stylistic edits to both of these letters.[188]

Actavis promptly responded on April 9, 2010.[189] Actavis confirmed "with a high degree of confidence" that the physicians in its database encompassed "all of the physicians that could have been exposed to the Comparison Detailer."[190] Regarding the Co-Pay materials, Actavis explained that it did not have the addresses of all consumers who received the brochure directly from physicians; thus, Actavis proposed mailing the "Dear

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[183] *Id*.
[184] ALLERGAN_MDL_01866384
[185] *Id*. at -86.
[186] *Id*.
[187] *Id*.
[188] *Id*. at -87–88.
[189] ALLERGAN_MDL_01399387.
[190] *Id*. at -88.

Consumer" letter to patients who received the Co-Pay materials directly from Actavis, and distributing the letters to physicians' offices along with a display stand.[191] Actavis agreed to incorporate the stylistic changes to both letters.[192]

The FDA responded on April 19, 2010.[193] The FDA generally agreed with Actavis's plan, but it recommended that Actavis include 100 copies of the "Dear Consumer" letter to each physician's office, and to make sure those letters were available for at least 90 days.[194] The FDA also offered further stylistic edits to the "Dear Consumer" letter.[195]

Actavis responded on May 3, 2010.[196] In this letter, Actavis agreed to disseminate 100 "Dear Consumer" letters to each physician's office.[197] Also, to ensure that sufficient copies of the letters were available during the 90-day period, Actavis committed to having its salesforce check the letters during each visit; Actavis also committed to calling each office that would not be physically visited to determine if additional letters were needed; and Actavis agreed to send an "instructional" letter to each physician containing a 1-800 number so that the physician could obtain additional copies if needed.[198] Actavis also agreed to accept the FDA's stylistic edits to the "Dear Consumer" letter.[199]

The FDA responded on May 20, 2010.[200] This time, the FDA recommended that Actavis representatives "physically visit each physician's office to set up and stock each

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[191] *Id*. at -88–89.
[192] *Id*. at -89.
[193] ALLERGAN_MDL_01874806.
[194] *Id*. at -08.
[195] *Id*.
[196] ALLERGAN_MDL_01875958.
[197] *Id*. at -59.
[198] *Id*.
[199] *Id*.
[200] ALLERGAN_MDL_01868671.

display stand" with Dear Consumer letters, and follow up with each physician's office through monthly telephone calls during the 90-day corrective period.[201]

Actavis responded on June 10, 2010.[202] In this letter, Actavis reaffirmed its commitment to mailing "Dear Consumer" letters to anyone who received Co-Pay materials directly from Actavis.[203] Actavis also revised its plan to reach consumers who may have received Co-Pay materials from physicians but never used them.[204] Specifically, there were about 10,000 physicians' offices and 558 pharmacies that received the Co-Pay materials, and Actavis agreed to physically visit each one and set up a stand with 25 copies of the "Dear Consumer" letter.[205] Moreover, Actavis would follow up with each physicians' office either physically or telephonically to ensure there were sufficient copies remaining.[206] To perform this corrective action, Actavis said that it would temporarily increase the size of its salesforce, training the sales representatives first.[207] In addition, Actavis informed the FDA that it discovered that its script for its telemarketing team tasked with calling physicians' offices and sending them Co-Pay materials contained similar language to that in the Comparison Detailer; Actavis revised this script, submitting it in Attachment 1.[208] Actavis also broadened the dissemination of its "Dear Healthcare Professional" letter to all physicians who received a "completed call" from the telemarketing team, meaning that the telemarketing representative was able to speak with someone at the physicians' office; the number of physicians who may have received either

[201] *Id*. at -73.
[202] ALLERGAN_MDL_01399410.
[203] *Id*.
[204] *Id*. at -11.
[205] *Id*.
[206] *Id*.
[207] *Id*.
[208] *Id*. at -12

a completed call or a personal visit from a sales representative was between 6,200 and 8,100.[209] Finally, Actavis revised its "Dear Healthcare Professional" and "Dear Consumer" letters to contain more consumer-friendly language.[210]

The FDA responded on July 6, 2010.[211] The FDA approved of Actavis's plan to send "Dear Consumer" letters to all healthcare professionals' offices (about 10,000 offices and 558 pharmacies) who may have received the Co-Pay materials.[212] The FDA also agreed with Actavis's plan to visit these offices physically, but it requested confirmation that Actavis would conduct monthly follow up with each pharmacy.[213] Regarding the "Dear Healthcare Professional" letter, the FDA agreed with Actavis's plan to mail letters to the 6,200 to 8,100 physicians who may have received either a completed call or materials personally from a sales representative.[214]

Actavis responded on July 16, 2010.[215] In this letter, Actavis confirmed that it would conduct follow up with each of the 558 pharmacies may have received Co-Pay materials.[216] Actavis also promised to send "Dear Healthcare Professional" letters to physicians who may have received either received either a completed call or a personal visit from a sales representative, which turned out to be 7,163 physicians.[217] Finally, Actavis submitted final versions of both letters.[218]

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[209] *Id*.
[210] *Id*.
[211] ALLERGAN_MDL_01869099.
[212] *Id*. at -01.
[213] *Id*.
[214] *Id*. at -02.
[215] ALLERGAN_MDL_01237743.
[216] *Id*. at -44.
[217] *Id*.
[218] *Id*.

The FDA responded on August 4, 2010.[219] In this letter, the FDA signed off on Actavis's plan, and requested that Actavis submit final letters on Form FDA-2253.[220] Actavis then retrained its salesforce on the corrective message[221] and the corrective information rollout plan.[222] During the corrective-action plan, Actavis's salesforce was not permitted to conduct normal promotional activities until further notice from Actavis.[223] Promotional activities resumed only if the sales representative completed disseminating corrective-action materials to his or her targets.[224]

On November 1, 2010, Actavis sent the FDA another letter.[225] In this letter, Actavis explained that it had completed disseminating the "Dear Healthcare Professional" and "Dear Consumer" letters, providing dates of completion.[226] Actavis also informed the FDA that it would begin conducting 30-day follow-up calls.[227]

Having reviewed the correspondence between the FDA and Actavis, internal communications at Actavis as well as with the contract salesforce, and deposition testimony (such as that by Terri Nataline, then Actavis's regulatory lead), I have drawn several conclusions about Actavis's corrective action plan.

First, Actavis promptly and aggressively undertook an extremely conservative, responsible and timely approach to the FDA's concerns. Faced with a number of options, including contesting the FDA's points in its warning letter, Actavis immediately sprang

[219] ALLERGAN_MDL_01238281.
[220] *Id*. at -82.
[221] ALLERGAN_MDL_01051295.
[222] ALLERGAN_MDL_00435497.
[223] ALLERGAN_MDL_01897894.
[224] ALLERGAN_MDL_01419292
[225] ALLERGAN_MDL_02106570.
[226] *Id*.
[227] *Id*. at -71.

into action in order to alleviate the FDA's concerns. It appropriately instructed the sales force to promptly cease any activity (and stop using any materials) that the FDA might find objectionable. Also, Actavis worked hand-in-hand with the FDA throughout to make sure the Agency approved of every detail of its efforts.

Second, the correspondence between the FDA and Actavis shows the intensive level of detail at which the FDA operates as a regulator. As set out above, the FDA was involved with every specific of the corrective action plan. Everything Actavis did in response to the warning letter was supervised and approved by the FDA.

Third, putting aside whether Actavis agreed with the FDA's concerns, the corrective action was comprehensive. The Dear Healthcare Professional and Dear Consumer letters were forthright, and they left no doubt what the FDA's position was on the materials implicated by the warning letter. Further, Actavis went to great lengths to disseminate the corrective message, including hiring additional individuals to its contract salesforce for this purpose.

D. The FDA took no further action, which indicates it was satisfied with the response.

If the FDA were not satisfied with Actavis's efforts and corrective action, it had a slew of enforcement techniques at its disposal, including product seizures,[228] injunctions,[229] and referrals for criminal prosecutions.[230] The FDA also could have filed suit in federal court through the Department of Justice.[231]

[228] 21 U.S.C. § 334
[229] 21 U.S.C. § 332
[230] 21 U.S.C. § 333.
[231] 21 U.S.C. § 335.

But the FDA did not do any of those things. Instead, as explained above, the FDA and Actavis worked closely to devise a corrective action plan, which the FDA approved. The absence of further action, combined with the iterative and cooperative approach undertaken by Actavis and the FDA, demonstrates that FDA approved of and was satisfied with Actavis's response and did not believe any further action was necessary or appropriate.

IX. LABELING

A. Generally

One of the FDA's most important roles in reviewing an NDA is to evaluate, influence and approve the new medication's Prescribing Information ("PI")—also sometimes referred to as the "package insert," "physician label," "professional labeling" or simply the "label"—according to regulations and guidance. As part of the NDA process, the applicant must submit draft labeling as part of its NDA submission.[232] As part of this process, the FDA carefully reviews the label word-for-word. The FDA is the final decision-maker on all product labeling, including on its content, format and language as well as on what information is and is not included; this determination is based on its independent review of the supporting data.[233] As the regulations make clear, the FDA's approval of an NDA means that the FDA's scientists and regulatory experts have determined that the medication is safe and effective when used in accordance with its labeling.[234] Before approving the NDA, the FDA "undertakes a detailed review of the proposed labeling, allowing only information for which there is a scientific basis to be

[232] 21 C.F.R. § 314.50(e)(2)(ii).
[233] 21 C.F.R. § 314.125(b)(2)-(8).
[234] 21 C.F.R. §§ 314.105, 314.125(b).

included in the FDA-approved labeling."[235] The "comprehensive scientific evaluation" that the FDA undertakes is "embodied in the labeling for the product which reflects thorough FDA review of the pertinent scientific evidence and communicates to health care practitioners the agency's formal, authoritative conclusions regarding the conditions under which the product can be used safely and effectively."[236]

After the NDA and the initial PI are approved by the FDA, the FDA continually reviews and often requires revisions to it based on post-marketing safety data as well as other information provided by the NDA holder and other sources. For example, under section 505(o)(4) of the Federal Food, Drug, and Cosmetic Act, the FDA is authorized to require safety labeling changes when it learns of "new safety information" it determines should be included.[237] All changes to labeling must be approved by the FDA as supplement applications to the medication's NDA. Each approval of a labeling change operates as a reaffirmation that the medication is safe and effective when used in accordance with its labeling.

Labeling changes can be undertaken by the NDA sponsor or required by the FDA. When the sponsor initiates the labeling change, the change nonetheless must be reviewed and approved by the FDA. The change can be submitted as a "Prior Review Application" ("PRA"), which require the FDA's review and approval before the change takes effect. Under certain circumstances, labeling changes can be submitted as a "Changes Being

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[235] 73 Fed. Reg. 49603 at 49604.

[236] *Id.*

[237] *See* 21 U.S.C. 355(o)(4); *Guidance for Industry[:] Safety Labeling Changes — Implementation of Section 505(o)(4) of the FD&C Act* at 3 ("Section 505(o)(4) authorizes FDA to require and, if necessary, ***order*** labeling changes if FDA becomes aware of new safety information that FDA believes should be included in the labeling of the drug."), available at https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm250783.pdf.

Effected" ("CBE") application, but if the change is implemented prior to FDA approval, the application holder risks the FDA concluding that the medication is "misbranded."[238] In addition, only certain types of changes may be implemented with a CBE, and those do not include, for example, changes to a Boxed Warning and most changes to the Highlights of Prescribing Information section of the PI and changes to a Medication Guide.[239]

Various regulations set out the FDA's labeling requirements for prescription medications. Those include 21 C.F.R. §§ 201.56 and 201.57.[240] For example, under § 201.56(a)(1)-(2), the labeling "must contain a summary of the essential scientific information needed for the safe and effective use of the drug" and "must be informative and accurate and neither promotional in tone nor false or misleading in any particular."

The FDA may require that certain contradictions or serious warnings may be presented in a Box. These are known as "boxed" warnings.[241] The FDA strictly regulates not only the content but the presentation of this warning; regulations require, for example, that "[t]he box must contain, in uppercase letters, a heading inside the box that includes the word 'WARNING' and conveys the general focus on the information in the box."[242] Likewise, "[t]he box must briefly explain the risk and refer to more detailed information in

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[238] *See Guidance for Industry[:] Public Availability of Labeling Changes in "Changes Being Effected" Supplements* at 1 n.1, available at https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm075091.pdf ("[A]fter revised labeling is submitted, the FDA carefully reviews the proposed change and then either approves it or sends a letter identifying the deficiencies with the proposed change. Of particular note, the Agency will not permit a labeling change that would misbrand the product.").
[239] *See id.*; *e.g.*, 21 C.F.R. §§ 314.70(b), (c)(6)(iii); *id.* at § 601.12(f)(2)-(3).
[240] The regulations governing the format of the labeling were revised in 2006. *See, e.g.*, 71 Fed. Reg. 3922 (Jan. 24, 2006).
[241] 21 C.F.R. § 201.57(c)(1) ().
[242] *Id.*

the 'Contraindications' or 'Warnings and Precautions' section, accompanied by the identifying number for the section or subsection containing the detailed information."[243]

B. At all times since Kadian®'s acquisition, its labeling has fully and appropriately warned of its risks.

I have evaluated various iterations of the Kadian® PI since Allergan's predecessor acquired the NDA in January 2009. Based on my review, I conclude that the Kadian® PI has at all times accurately and appropriately presented the medication's potential risks—including those of overdose and death—such that prescribing physicians could consider the risks and benefits of prescribing Kadian® to particular patients. I determine that it did.

Shortly after acquiring Kadian®, Allergan's former affiliate revised the PI to reflect the change in ownership.[244] This first version of the Kadian® PI while the medication was owned by an Allergan affiliate or former affiliate contains robust risk warnings and disclosures.[245] Foremost, it (and all iterations of the Kadian® PI in effect at any point when any current or former Allergan affiliate owned Kadian®) has contained a Boxed Warning.[246] The Boxed Warning states, for example, in all bold that "KADIAN® contains morphine sulfate, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. KADIAN® can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing KADIAN® in situations where the physician or pharmacist is concerned about

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[243] *Id.*

[244] *See* Kadian PI (revised February 2009), ALLERGAN_MDL_02200691. Changes included changing the language "Kadian® is a registered trademark owned by Alpharma Branded Products Division Inc." to "Kadian® is a registered trademark of Actavis Elizabeth LLC." *Compare id.* with Kadian PI (revised March 2007), available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2007/020616s025lbl.pdf.

[245] *See* Kadian PI (revised February 2009), ALLERGAN_MDL_02200691.

[246] *Id.* at ALLERGAN_MDL_02200691.

an increased risk of misuse, abuse or diversion."[247] Numerous other warnings appear throughout the PI.[248]

The February 2009 version of the Kadian® PI also sets out the FDA's then-current indication for extended-release opioid medications such as Kadian®: "KADIAN® capsules are an extended-release oral formulation of morphine sulfate indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time."[249] This indication was neither chosen by Allergan nor specific to Kadian®; the FDA required it for several extended-release opioids until 2013, when the FDA revised it (as described below).

These risk disclosures would only be strengthened from this already detailed, robust version, particularly as Allergan's current and former affiliates appropriately responded to requests from the FDA, as described below. The next update to the Kadian® PI took place in February 2010, when it was revised to change an additional reference from "Alpharma" (the prior owner) to "Actavis."[250] After February 2010, the PI remained the same for approximately two years, until July 2012.[251]

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[247] *Id.*

[248] *See generally id.*

[249] *Id.* at ALLERGAN_MDL_02200697.

[250] *See* May 10, 2010 Email (ALLERGAN_MDL_01132981) ("Please find attached the new revision of the insert for KADIAN Morphine Sulfate Extended-Release Capsules which was revised to remove the reference to 'Alpharma' in the Dosage and Administration section.") and Attachment (ALLERGAN_MDL_01132982) (February 2010 Kadian® PI); *Summary of Labeling Changes* from 2010 Kadian® Annual Report, ALLERGAN_MDL_02200678 at ALLERGAN_MDL_02200680 (indicating that "Reason" for revision to PI between February 2010 and February 2009 was: "All references to 'Alpharma' within the insert text have been updated to 'Actavis'.").

[251] *See Summary of Labeling Changes* from 2011 Kadian® Annual Report, ALLERGAN_MDL_02199040 at ALLERGAN_MDL_02199042 (indicating no change to PI since February 2010); *Summary of Labeling Changes* from 2012 Kadian® Annual Report, ALLERGAN_MDL_02209819 at ALLERGAN_MDL_02209821 (indicating next revision to Kadian® PI took place in July 2012).

The next revision, in July 2012, was the result of three supplemental new drug applications ("sNDAs") submitted by Actavis Elizabeth, LLC, which the FDA coordinated such that the changes would be merged into one revised PI.[252] On July 9, 2012, the FDA approved all three sNDAs. The first sNDA, S-036, involved converting the PI into a new labeling format—known as the "Physicians Labeling Rule (PLR) format"—set out in 21 C.F.R. § 201.56 and 21 C.F.R. § 201.57 (*see supra* § IX.A).[253] The second sNDA, S-041, concerned the REMS for Kadian® (*see infra* § X) as well as associated labeling changes, including the addition of a Medication Guide (*see infra* § IX.D).[254] The third sNDA, S-044, included additional intermediate dosage strengths for Kadian® and associated labeling changes.[255] The resulting July 2012 version of the Kadian® PI reflects all of those changes.[256]

That same month, in July 2012, PROP submitted the Citizen Petition described above (*see supra* § VII.C),[257] to which the FDA responded in September 2013.[258] In its response, the FDA stated that it was taking several actions, including some labeling

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[252] *See* April 19, 2012 Email from FDA, ALLERGAN_MDL_00804259 at ALLERGAN_MDL_00804260 ("As you know, we have 3 pending supplements for Kadian in house right now: S-036 (PLR Conversion)[;] S-041 (REMS supplement)[;] S-044 (CMC: additional strengths)[.] All of these supplements involve labeling changes. We want to coordinate the approval of all of these supplements so that all of the labeling changes are merged into one label.").

[253] *See* July 9, 2012 Letter from FDA re NDA 020616/S-036, S-044, ALLERGAN_MDL_00517082.

[254] *See* July 9, 2012 Letter from FDA re NDA 020616/S-041, available at https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2012/020616Orig1s041ltr.pdf.

[255] *See* July 9, 2012 Letter from FDA re NDA 020616/S-036, S-044, ALLERGAN_MDL_00517082.

[256] Kadian PI (revised July 2012), available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/020616s041lbl.pdf.

[257] *See* June 25, 2012 PROP Citizen Petition to FDA.

[258] September 10, 2013 FDA Response to PROP Citizen Petition, available at http://www.supportprop.org/wp-content/uploads/2014/12/FDA_CDER_Response_to_Physicians_for_Responsible_Opioid_Prescribing_Partial_Petition_Approval_and_Denial.pdf.

changes for extended-release opioid medications like Kadian® (though not to the extent PROP had requested).[259] The FDA announced that it was making these changes pursuant to its authority under section 505(o)(4) of the Act, which authorizes the FDA to require application holders to make what are known as "safety labeling changes" when it becomes aware of "new safety information."[260] *First*, the FDA required the addition of more information to the boxed warning "to give greater emphasis and prominence to the risks of misuse, abuse, NOWS, addiction, overdose, and death."[261] *Second*, and most significant, the FDA changed the wording of the indication.[262] While previously (as noted above) Kadian® and other extended-release, long-acting opioids were "indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time," the revised language stated that these medications are "indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate."[263] This new "framework," per the FDA, would "allow[] prescribers to

[259] *Id.* at 6-10.
[260] *Id.* at 6 & n.28 ("*New safety information* is information derived from a clinical trial, an adverse event report, a post-approval study (including a study under section 505(o)(3) of the FD&C Act), or peer-reviewed biomedical literature; data derived from the post-market risk identification and analysis system under section 505(k) of the FD&C Act; or other scientific data deemed appropriate by the Agency about, among other things, a serious or an unexpected serious risk associated with use of the drug of which the Agency has become aware (that may be based on a new analysis of existing information) since the drug was approved, the REMS was approved, or since the last assessment of the approved REMS; or the effectiveness of the approved REMS for the drug obtained since the last assessment of such strategy.").
[261] *Id.* at 7 ("For example, the first sentence of the new boxed warning provides that ER/LA opioids 'expose patients and other users to the risks of opioid addiction, abuse, and misuse which can lead to overdose and death.' The new boxed warning also urges prescribers to 'assess each patient's risk' before prescribing, and to 'monitor all patients regularly for the development of these behaviors or conditions.'").
[262] *Id.* at 7.
[263] *Id.* at 8.

make an assessment of pain relative to a patient's ability to perform daily activities or enjoy a reasonable quality of life, not only on where a patient's pain falls on an intensity scale, and assess if ER/LA opioids are needed after determining whether (a) the pain is severe enough to require daily, around-the-clock, long-term opioid treatment, and (b) if alternatives to ER/LA opioids are inadequate to manage such pain, in light of the serious risks associated with ER/LA opioid analgesics."[264] *Third*, the FDA announced several required changes to the Dosage and Administration, Warnings and Precautions, Drug Interactions, and Use in Specific Populations sections of the labeling as well as to the Patient Counseling Information and the product-specific Medication Guides.[265]

Notably, these changes reflect the FDA's emphasis on the importance of the prescriber in determining whether an opioid is required in each individual patient's case, and if so in what dosage, for what length, and other aspects of treatment. The FDA expressed the intent that all of these changes would "encourage[e] better prescribing, monitoring, and patient counseling practices involving these drugs."[266] For example, with respect to the change to the indication, the FDA stated that the revisions was intended to "prompt prescribers to more closely assess each individual patient's condition, and carefully evaluate whether alternative treatment options such as non-opioid analgesics or IR opioids are appropriate" as well as to "reflect that ER/LA opioid analgesics should be prescribed only when the prescriber determines that such alternatives are ineffective, not tolerated, or would otherwise be inadequate."[267] Likewise, with respect to the third set of

[264] *Id.*
[265] *Id.* at 8-9.
[266] *Id.* at 6.
[267] *Id.* at 8.

changes noted above, the FDA expressly stated that these revisions were "specifically intended to urge prescribers to weigh carefully whether the benefits of the ER/LA opioid outweigh its serious risks on a patient-by-patient basis."[268]

On the same date as the response to the PROP Citizen Petition—September 10, 2013—the FDA sent a letter to Watson Laboratories, Inc. as the then-holder of Kadian®'s NDA notifying it of these changes.[269] The FDA required Kadian®'s application holder to submit these changes under an sNDA,[270] which the FDA then approved by letter dated April 16, 2014.[271] The resulting PI—the version revised April 2014—reflects all of the changes required by the FDA.[272]

The next revision to the Kadian® PI occurred in December 2016.[273] This revision was prompted by two Safety Labeling Change Notifications required by the FDA pursuant to section 505(o)(4) of the Federal Food, Drug, and Cosmetic Act as a result of new safety information.[274] *First*, by letter dated March 22, 2016 to Allergan Sales, LLC (the current holder of Kadian®'s NDA), the FDA required the strengthening of the risk disclosures regarding several areas, namely "serotonin syndrome following the initiation of an opioid in patients who had previously been taking one or more serotonergic drugs," "the occurrence of adrenal insufficiency in patients following the initiation of an opioid,"

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[268] *Id.*

[269] *See* September 10, 2013 FDA Letter, ALLERGAN_MDL_01291325 at ALLERGAN_MDL_01291330 to ALLERGAN_MDL_01291342.

[270] *Id.*

[271] *See* April 16, 2014 FDA Letter, available at https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2014/020616Orig1s051ltr.pdf.

[272] *See* Kadian® PI (revised April 2014), available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/020616s051lbl.pdf.

[273] *See* Kadian® (revised December 2016), available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020616s057lbl.pdf.

[274] *See Summary of Labeling Changes* from 2017 Kadian® Annual Report, ALLERGAN_MDL_02197022 at ALLERGAN_MDL_02197023.

"androgen deficiency in patients with long-term exposure to opioids."[275] *Second*, by letter dated August 31, 2016, the FDA notified Allergan Sales, LLC of several additional changes based on "new safety information" under Section 505(o)(4), namely those related to the concomitant use of opioid medications and benzodiazepines or other central nervous system depressants (*e.g.*, alcohol).[276] For example, a specific warning about the use of benzodiazepines and other CNS depressants along with Kadian® was to be added to the boxed warning.[277] In both cases, these changes demonstrate the FDA exercising its important authority under section 505(o)(4) to react to "new safety information" (as that term is used in the Act) to require changes to medications' labeling to provide prescribers (as well as patients) with additional information that could be helpful to them in determining whether and how to prescribe opioid medications. On December 16, 2016, the FDA approved Allergan Sales, LLC's sNDA to implement these changes.[278] The Kadian® PI reflecting these changes was revised as of December 2016.[279]

There were no changes between December 2016 and September 2018. The September 2018 version of the PI—which was approved by the FDA by letter dated

[275] March 22, 2016 FDA Letter, ALLERGAN_MDL_02195310.
[276] August 31, 2016 FDA Letter, ALLERGAN_MDL_02195190.
[277] *Id.* at ALLERGAN_MDL_02195191. Corresponding risk information was to be added to the Warnings and Precautions and Drug Interactions and Patient Counseling Information sections of the PI as well as to the Medication Guide. *Id.* at ALLERGAN_MDL_02195191 to ALLERGAN_MDL_02195193.
[278] *See* December 16, 2016 FDA Letter, available at https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2016/020616Orig1s057ltr.pdf.
[279] *See* Kadian® PI (revised December 2016), available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020616s057lbl.pdf.

September 18, 2018[280]—is the version of the Kadian® PI in effect as of the date of this report.[281]

The FDA-approved September 2018 PI contains a wealth of information about Kadian® for the consideration of physicians in determining whether to prescribe Kadian® and, if so, under what limitations.[282] For example, the boxed warning alone spans more than a page and sets out the following, unmistakably bold warnings:[283]

WARNING: ADDICTION, ABUSE, AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; INTERACTION WITH ALCOHOL; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Addiction, Abuse, and Misuse
KADIAN exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing KADIAN, and monitor all patients regularly for the development of these behaviors and conditions [*see Warnings and Precautions* (5.1)].

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)
To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a REMS for these products *[see Warnings and Precautions (5.2)]*. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to

- **complete a REMS-compliant education program,**
- **counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products,**
- **emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and**
- **consider other tools to impove patient, household, and community safety.**

Life-Threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with use of KADIAN. Monitor for respiratory depression, especially during initiation of KADIAN or following a dose increase. Instruct patients to swallow KADIAN capsules whole or to sprinkle the contents of the capsule on applesauce and swallow immediately without chewing. Crushing, chewing, or dissolving the pellets in KADIAN capsules can cause rapid release and absorption of a potentially fatal dose of morphine *[see Warnings and Precautions (5.3)]*.

Accidental Ingestion
Accidental ingestion of even one dose of KADIAN, especially by children, can result in a fatal overdose of morphine *[see Warnings and Precautions (5.3)]*.

Neonatal Opioid Withdrawal Syndrome
Prolonged use of KADIAN during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be

[280] *See* September 18, 2018 FDA Letter, available at https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2018/020616Orig1s061s062ltr.pdf.
[281] *See* Kadian® PI (revised September 2018), available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/020616s061s062lbl.pdf.
[282] *Id.*
[283] *Id.* at 3-4.

available *[see Warnings and Precautions (5.4)]*.

Interaction with Alcohol

Instruct patients not to consume alcoholic beverages or use prescription or nonprescription products that contain alcohol while taking KADIAN. The co-ingestion of alcohol with KADIAN may result in increased plasma levels and a potentially fatal overdose of morphine [*see Warnings and Precautions (5.5)*].

Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants

Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death [*see Warnings and Precautions (5.5), Drug Interactions (7)*]

- **Reserve concomitant prescribing of KADIAN Injection and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.**
- **Limit dosages and durations to the minimum required.**
- **Follow patients for signs and symptoms of respiratory depression and sedation.**

Prominent among the warnings, there is also a full section on "Addiction, Abuse, and Misuse" that clearly states, for example, that "[a]lthough the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed KADIAN" and that "[a]ddiction can occur at recommended doses and if the drug is misused or abused."[284] The PI also discloses, in no uncertain terms, the risks of "serious, life-threatening, or fatal respiratory depression," which are present "even when used as recommended."[285] The PI also reflects each of the various warnings added by the FDA pursuant to identified "new safety information" under section 505(o)(4) of the Federal Food, Drug, and Cosmetic Act (described above), such as the risk of concomitant use with benzodiazepines and other central nervous system depressants.[286] In light of these and other risks, physicians are instructed to "[a]ssess each patient's risk for opioid addiction, abuse, or misuse prior to prescribing KADIAN, and monitor all patients receiving KADIAN for the development of these behaviors and conditions."[287]

The PI also informs physicians about the REMS (*see infra* § X) as a resource from which prescribers can more additional FDA-vetted information, stating, for example, that

[284] *Id.* at 9.
[285] *Id.* at 10.
[286] *See generally id.*
[287] *Id.* at 9.

referring prescribers to websites with information on the REMS as well as the accredited REMS continuing medical education.[288] Similarly, the current Kadian® PI sets out some of the clinical trial results for physicians to review and consider in conjunction with the other information in the PI.[289]

Recognizing the critical role that patients play in their own treatment, the current Kadian® PI contains information that prescribers are encouraged to provide to their patients.[290] In addition to instructing prescribers to "[a]dvise the patient to read the FDA-approved patient labeling," the PI encourages physicians to inform patients about, among other things, the following:[291]

- "Addiction, Abuse, and Misuse[:] Inform patients that the use of KADIAN, even when taken as recommended, can result in addiction, abuse, and misuse, which can lead to overdose and death. . . . Instruct patients not to share KADIAN with others and to take steps to protect KADIAN from theft or misuse."
- "Life-Threatening Respiratory Depression[:] Inform patients of the risk of life-threatening respiratory depression, including information that the risk is greatest when starting KADIAN or when the dosage is increased, and that it can occur even at recommended doses[.] Advise patients how to recognize respiratory depression and to seek medical attention if breathing difficulties develop."

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[288] *Id.* at 9-10.
[289] *Id.* at 14-16, 27-29.
[290] *Id.* at 31-33. All versions of the Kadian® PI since the medication was acquired have contained information intended to be passed on to patients. *E.g.*, Kadian® PI (revised February 2009), ALLERGAN_MDL_02200691 at ALLERGAN_MDL_02200701 to ALLERGAN_MDL_02200702 ("If clinically advisable, patients receiving KADIAN®, or their caregivers should be given the following information by the physician, nurse, or pharmacist . . .").
[291] *See* Kadian® PI (revised September 2018) at 31-33, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/020616s061s062lbl.pdf.

- "Disposal of Unused KADIAN[:] Advise patients to flush the unused capsules down the toilet when KADIAN is no longer needed."

Especially when combined with the Medication Guide that is provided to patients (described below in § IX.D), this and other information in the Kadian® PI leaves no doubt as to the risks of prescribing and using this medication, and puts proper emphasis on the seriousness of those risks.

Notably, at all times the Kadian® PI has included an indication for its use for chronic pain. The first version after Allergan's then-affiliate acquired the medication stated that it was "indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an ***extended period of time***."[292] Beginning with the April 2014 version, the FDA-approved indication has been for "the management of pain severe enough to require daily, around-the-clock, ***long-term*** opioid treatment and for which alternative treatment options are inadequate."[293] At no point has the FDA-approved indication limited Kadian®'s use to chronic cancer—as distinguished from non-cancer—pain.

C. Norco®'s PI has also appropriately communicated its risks to prescribers.

I have also evaluated a number of iterations of the Norco® PI to determine whether they accurately and appropriately presented the medication's potential risks such that

[292] *See* Kadian PI (revised February 2009), ALLERGAN_MDL_02200691 at ALLERGAN_MDL_02200697 (emphasis added).

[293] *See* Kadian® PI (revised April 2014), available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/020616s051lbl.pdf (emphasis added); *see also* July 11, 1997 FDA Medical Officer Review, Kessler Dep. Ex. 45 at 1 (FDA: "The drug was approved by FDA in 1996 for use in patientis with chronic, moderate-to-severe pain who require repeated dosing with a potent opioid analgesic.").

prescribing physicians could consider the risks and benefits of prescribing Norco® to particular patients. I conclude that they did.

The Norco® PIs approved by the FDA in conjunction with the original approval of the two Norco® ANDAs, contained clear risk warnings that would only get stronger over time. The PI approved with ANDA 040148[294] stated, for example, "**WARNING:** May be habit forming."[295] Similarly, it stated that "[a]t high doses or in sensitive patients, hydrocodone patients may produce dose-related respiratory depression by acting directly on the brain stem respiratory center" and that "[h]ydrocodone also affects the center that controls respiratory rhythm, and may produce irregular and periodic breathing."[296] Similarly, it stated that "[p]sychic dependence, physical dependence, and tolerance may develop upon repeated administration of narcotics."[297] The labeling for the other Norco® ANDA, 040099—which was sponsored by an unaffiliated third party and was only acquired by Watson several years later—contained similar statements.[298] So too did subsequent revisions of the Norco PIs (of which, until they were recently combined into one, there were different versions for different strengths).[299]

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[294] *See* Norco® ANDA 040148 FDA Approval Information, ALLERGAN_MDL_04161107 at ALLERGAN_MDL_04161118.
[295] *Id.*
[296] *Id.*
[297] *Id.*
[298] *See* Norco® ANDA 040099 FDA Approval Information, ALLERGAN_MDL_04161130 at ALLERGAN_MDL_04161140 to ALLERGAN_MDL_04161141.
[299] *E.g.*, Norco® PI (revised April 2002) (7.25/325 and 10/325 strengths), ALLERGAN_MDL_01095947; Norco® PI (revised April 2003) (5/325 strengths), ALLERGAN_MDL_01095940; Norco® PI (revised July 2007) (7.5/325 and 10/325 strengths), ALLERGAN_MDL_01680965; Norco® PI (revised June 2011) (7.5/325 and 10/325 strengths), ALLERGAN_MDL_02210219; Norco® PI (revised August 2012) (7.5/325 and 10/325 strengths), ALLERGAN_MDL_01768757; Norco® PI (revised August 2013) (7.5/325 and 10/325 strengths), ALLERGAN_MDL_02210402; Norco® PI (revised August 2014) (2.5/325 strength), available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/040148s053lbl.pdf; Norco® PI (revised August 2014) (7.5/325 and 10/325 strengths), available at available at

Like the current Kadian® PI, the current Norco® PI (revised September 2018) contains a robust set of risk warnings as well as ample other information for physicians.[300] For example, among many other warnings, it contains a boxed warning.[301] Likewise, the current indication makes clear that Norco® should only be prescribed where other options are inadequate: "Norco® is indicated for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate."[302] Further, the Norco® PI also contains information about REMS as well as information intended to be provided by prescribers to patients.[303]

I conclude that the Norco® labeling (especially as combined with its Medication Guide, described below) leaves no doubt to either prescribers or patients of the serious risks of this medication. As the FDA recognizes, it is up to prescribers (and, ultimately, patients) whether an opioid medication like Norco® should be prescribed and used in the context of each individual patient, and, if so, how.

D. Another aspect of both Kadian®'s and Norco®'s labeling is their Medication Guides, which provide clear risk information to patients.

Medication Guides are another component of the FDA-approved labeling for some medications.[304] While PIs are written primarily for healthcare professionals like physicians, Medication Guides contain information intended for patients about how to

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https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/040148s053lbl.pdf; Norco® PI (revised August 2014) (5/325 strength), available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/040099Orig1s018lbl.pdf; Norco® PI (revised February 2017) (all strengths), ALLERGAN_MDL_02219168; Norco® PI (revised May 2018) (all strengths), available at https://www.allergan.com/assets/pdf/norco_pi.

[300] Norco® PI (revised September 2018), available at https://www.allergan.com/assets/pdf/norco_pi.

[301] *Id.* at 1-2.

[302] *Id.* at 6.

[303] *Id.* at 7, 11-13.

[304] 21 C.F.R. § 208.1.

safely use a medication. Medication Guides intended to be provided to the patient each time the medication is prescribed.[305] The information in the Medication Guide is intended to supplement—not supplant—oral counseling from health care professionals such as physicians.[306] Medication Guides are intended to help "provid[e] information necessary for patients to use their medications safely and effectively."[307] The FDA must approve each Medication Guide before it is distributed.[308]

Per the regulations, Medication Guides "shall be written in English, in nontechnical, understandable language."[309] They must also be "scientifically accurate" and must be consistent with the physician labeling.[310] They are also required to "be specific and comprehensive."[311] As set out below, and as is the case here, the FDA can require Medication Guides as an element of a Risk Evaluation and Mitigation Strategy, in which case the Medication Guide is also subject to additional regulatory requirements.[312]

Both Kadian® and Norco® have Medication Guides. Written in clear, plain English, Kadian®'s current Medication Guide describes the medication as "[a] strong prescription pain medicine that contains an opioid (narcotic) that is used to manage pain severe enough to require daily around-the-clock, long-term treatment with an opioid, when other pain treatments such as non-opioid pain medicines or immediate-release opioid

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[305] 21 C.F.R. § 208.24 (e) ("Each authorized dispenser of a prescription drug product for which a Medication Guide is required under this part shall, when the product is dispensed to a patient (or to a patient's agent), provide a Medication Guide directly to each patient (or to the patient's agent) unless an exemption applies under 208.26."); *see also id.* at § 208.26 (setting out limited "[e]xemptions and deferrals").
[306] 63 Fed. Reg. 66378.
[307] *Id.*
[308] *See* 21 C.F.R. 208.24(a).
[309] 21 C.F.R. § 208.20(a)(1).
[310] 21 C.F.R. § 208.20(a)(2).
[311] 21 C.F.R. § 208.20(a)(3).
[312] 21 U.S.C. § 355-1(e)(2), (g) & (h).

medicines do not treat your pain well enough or you cannot tolerate them."[313] Also, it states that Kadian® "can put you at risk for overdose and death," which can occur "[e]ven if you take your dose correctly as prescribed."[314] Patients are also instructed to "[n]ever give anyone else your KADIAN," as "[t]hey could die from taking it."[315] Norco®'s current Medication Guide contains similar information.[316]

In both cases, the information in the Medication Guides is an instructive supplement to the full PI described above that provides important information written in an unambiguous, clear way understandable by lay persons.

X. ALLERGAN'S PARTICIPATION IN REMS

A. Overview and Significance of REMS

Under the Food and Drug Administration Amendments Act of 2007 (the "FDAAA"), the FDA was granted authority, effective March 25, 2008, to require Risk Evaluation and Mitigation Strategies ("REMS"). The FDA may require a REMS for a product or class of products to help "ensure that the benefits of the drug outweigh the risks of the drug."[317] REMS may be required either before or after approval of the medicine.[318] They can be required either for a single medicine or a class of medicines.

A REMS program can include several "elements." These elements, several of which are described in more detail below, include Medication Guides (*see supra* § IX.D),

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[313] Kadian® Medication Guide (revised December 2016), available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/020616s061s062lbl.pdf (pages 34 and 35).
[314] *Id.*
[315] *Id.*
[316] Norco® Medication Guide (revised June 2018), available at https://www.allergan.com/assets/pdf/norco_pi (pages 25 and 26).
[317] 21 U.S.C.A. § 355-1(a)(1).
[318] *Id.* at § 355-1(a)(1)-(2).

Patient Package Inserts, a Communication Plan and elements to assure safe use ("ETASU").[319] In turn, ETASUs can include, where appropriate, components such as the requirement that "pharmacies, practitioners, or health care settings that dispense the drug are specially certified."[320] REMS participants must also submit regular assessments of the REMS to the FDA, which is one way in which the FDA monitors the progress of the program.[321]

The FDA ultimately determines which is elements is necessary. Application holders of medications work closely with the FDA to develop REMS programs. If appropriate, those programs are then approved by the FDA.

B. Allergan has participated in the REMS for extended-release, long-acting opioids.

In February 2009, the FDA sent Actavis Elizabeth, LLC (a former Allergan affiliate that then held the NDA for Kadian®) a letter informing it that the FDA was requiring a REMS for certain opioid products, including Kadian®.[322] This class-wide program would be known as the Extended Release and Long-Acting Opioids ("ER/LA") REMS. The new REMS, per the FDA's letter, would "ensure that the benefits of the drugs continue to outweigh the risks of: 1) use of certain opioid products in non-opioid-tolerant individuals; 2) abuse; and 3) overdose, both accidental and intentional."[323] The FDA invited Actavis Elizabeth, LLC and the other sponsors to meeting to "discuss how such a program can best be designed to manage the risks."[324]

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[319] *Id.* at § 355-1(e)-(f).
[320] *Id.* at § 355-1(f)(3).
[321] *Id.* at § 355-1(d).
[322] February 6, 2009 FDA Letter, ALLERGAN_MDL_01774195.
[323] *Id.* at ALLERGAN_MDL_01774195.
[324] *Id.*

The meeting, which two representatives from Actavis attended, took place on March 3, 2009.[325] After the meeting, the FDA opened a public docket in order to solicit comments and input from the public.[326] This was one step the FDA would take over the months and years that the FDA took to consider the input of the public.

After holding a number of "stakeholder, industry, and public meetings, and Advisory Committee meetings" throughout 2009 and 2010, the FDA sent Actavis Elizabeth, LLC a letter notifying it of the elements of the proposed ER/LA REMS in April 2011.[327] The FDA sent similar letters to other application holders of ER/LA opioids.[328] The letter to Actavis Elizabeth, LLC stated that the REMS would be a "single, shared system" that would be "used to implement the REMS for all members of the class."[329] The elements of the shared ER/LA program would include a Medication Guide, Elements to Assure Safe Use ("ETASU"), and the submission of "assessments" at regular intervals that would "assess the extent to which the elements to assure safe use are meeting the goals of [the] REMS and whether the goals or elements should be modified."[330] More specifically,

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[325] *See* March 9, 2009 Email Chain with FDA, ALLERGAN_MDL_00672481 at ALLERGAN_MDL_00672482 ("Please be advised that Monique Weitz and I, Terri Nataline [Vice President, Regulatory and Medical Affairs], will represent Actavis US at the March 3rd meeting . . .").

[326] *See* FDA Presentation on *Development of the 2012 Extended Release and Long-Acting (ER/LA) Opioid Analgesic REMS*, available at https://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM539363.pdf, at 4 ("FDA received 2617 comments on the proposed REMS.").

[327] *See* April 18, 2011 FDA Letter, ALLERGAN_MDL_01773409 at ALLERGAN_MDL_01773409.

[328] *See* FDA Presentation on *Development of the 2012 Extended Release and Long-Acting (ER/LA) Opioid Analgesic REMS*, available at https://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM539363.pdf, at 8.

[329] *See* April 18, 2011 FDA Letter, ALLERGAN_MDL_01773409 at ALLERGAN_MDL_01773410.

[330] *Id.* at ALLERGAN_MDL_01773410 to ALLERGAN_MDL_01773411.

the ETASU was to include, per the FDA, training for prescribers, the provision of information that prescribers "can use to educate patients in the safe use, storage, and disposal of opioids," and that sponsors were to "inform prescribers of the existence of the REMS and the need to successfully complete the necessary training."[331]

The FDA was clear that the various companies should work together to design, implement and carry out the ER/LA REMS.[332] As required, the participating companies—often referred to as the "REMS Program Companies"—entered into the "Opioid REMS Program Agreement" as of May 2012. The agreement provided that an entity then known as Campbell Alliance Ltd. would provide day-to-day project management services to the participants.[333] Current and former affiliates of Allergan have been among the signatories to this agreement.[334]

On July 9, 2012,[335] the FDA approved the ER/LA REMS.[336] Per the FDA's approval letter to Actavis Elizabeth, LLC, the approved REMS "consists of a Medication Guide, elements to assure safe use, and a timetable for submission of assessments of the

[331] *Id.* at ALLERGAN_MDL_01773410.
[332] *E.g.*, *id.* at ALLERGAN_MDL_01773410 ("FDA strongly recommends that sponsors make provision in the single shared system for joint assessments of the effectiveness of the REMS.").
[333] *See Opioid REMS Program Agreement*, ALLERGAN_MDL_02823086. The Agreement has since been modified and amended.
[334] *See id.* at ALLERGAN_MDL_02823102 (listing an Actavis entity as the participant for, *inter alia*, Kadian®).
[335] Between the acquisition of Kadian® and the approval of the REMS, Actavis had FDA-approved Risk Management Plan to help address the risks associated with the medication. *E.g.*, Risk Management Plan (Version 3.0) (Oct. 13, 2009), ALLERGAN_MDL_00816623; Risk Management Plan Version 3.0, Annual Report, ALLERGAN_MDL_00640824. This program was replaced by the ER/LA REMS.
[336] *See* FDA Presentation on *Development of the 2012 Extended Release and Long-Acting (ER/LA) Opioid Analgesic REMS*, available at https://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM539363.pdf, at 13 ("FDA considered comments received and approved the ER/LA Opioid Analgesics REMS on July 9, 2012.").

REMS.[337]

The first of these elements is the Medication Guide. Medication Guides, which are provided directly to patients, contain plain English information about the risks and proper use of the medication to supplement the information provided by the prescriber. *See supra* IX.D. The first version of Kadian®'s Medication Guide, which the FDA approved in July 2012, plainly states, for example, that "KADIAN® overdose can cause life threatening breathing problems that can lead to death."[338]

Another of the required elements of the ER/LA REMS is the scheduled assessments. These assessments are required at set intervals.[339] Each "shall include, with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether 1 or more such goals or such elements should be modified."[340] In this case, Allergan and the other participating companies have regularly submitted the requisite assessments to the FDA, as required.[341] These assessments contain detailed information about the progress of the REMS—including, for example, information about the status of prescriber education efforts—that the FDA can then use to evaluate the REMS and whether changes are required.

The third element of the ER/LA REMS is the ETASU. Pursuant to this element,

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[337] *See* July 9, 2012 FDA Letter, available at https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2012/020616Orig1s041ltr.pdf.

[338] *See* Kadian Labeling (revised July 2012), available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/020616s041lbl.pdf.

[339] *See* 21 U.S.C.A. § 355-1(d).

[340] *Id.* at § 355-1(g)(3).

[341] *E.g.*, *Twelve-Month FDA Assessment Report* (June 27, 2013), ALLERGAN_MDL_01185455; *Twenty-Four Month FDA Assessment Report* (June 26, 2014), ALLERGAN_MDL_01336058; *Thirty-Six Month FDA Assessment Report* (September 22, 2015), ALLERGAN_MDL_02426801; *Forty-Eight Month FDA Assessment Report* (August 26, 2016), ALLERGAN_MDL_02412877.

the REMS participants have provided training to health care providers about (among other subjects) the proper prescription of opioids, including on their risks. The training must be based on the FDA-approved "Blueprint," which "contains core messages to be conveyed to prescribers in the training about the risks and appropriate prescribing practices for the safe use of ER/LA opioid analgesics."[342] The current version of the Blueprint[343] contains a wealth of information for health care providers about opioid medications, the treatment of pain, and related subjects, such as "[h]ow to assess patients in pain, identifying risk factors for abuse and addiction" as well as "[t]he fundamental elements of addiction medicine."[344]

The participating companies maintain a publicly available website with information on how health care providers can access this training: www.ER-LA-opioidREMS.com. They have also directly mailed letters to prescribers (specifically those who have registered to prescribe scheduled drugs) to notify them of a number of REMS components, including the availability of training.[345]

These educational materials are subject to audits by "an auditor independent of the NDA/ANDA holders."[346] These audits evaluate, for example, "whether the content of the training covers all components of the FDA Blueprint approved as part of the REMS" as

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[342] August 19, 2014 FDA Letter and Attachment, ALLERGAN_MDL_01153815 at ALLERGAN_MDL_01153820.

[343] *See FDA Education Blueprint for Health Care Providers Involved in the Treatment and Monitoring of Patients with Pain* (September 2018), available at https://www.accessdata.fda.gov/drugsatfda_docs/rems/Opioid_analgesic_2018_09_18_FDA_Blueprint.pdf.

[344] *Id.*

[345] *See, e.g.*, *Dear Healthcare Provider Letter #1*, available at https://opioidanalgesicrems.com/RpcUI/rems/pdf/resources/Dear_Healthcare_Provider_Letter_1.pdf.

[346] August 19, 2014 FDA Letter and Attachment, ALLERGAN_MDL_01153815 at ALLERGAN_MDL_01153820.

well as "for training conducted by CE providers, whether the training was conducted in accordance with the standards for CE of the Accreditation Council for Continuing Medication Education (ACCME), or of another CE accrediting body appropriate to the prescribers' medical specialty or healthcare profession."[347]

Also, as part of the ETASU, the FDA has approved a Patient Counseling Document ("PCD").[348] The PCD is intended to help prescribers discuss the risks and benefits of opioid use with their patients. The PCD is also intended to be given to patients. Like the Medication Guide, the PCD is written in clear terms. For example, it plainly states that "[o]pioids have serious risks of addiction and overdose" and that (in bold) "[t]oo much opioid medicine in your body can cause your breathing to stop - which could lead to death."[349]

I draw several conclusions from Allergan's participation in the FDA-required REMS. *First*, REMS is another program by which the FDA helps ensure the safety and proper prescription as well as use of opioid pain medications. The FDA is heavily involved in every aspect of the REMS; every component is scrutinized and approved by the FDA before it is implemented.

Second, the REMS program reflects the FDA's acknowledgment of the important role that prescribers and patients play in the proper use of opioids. As the FDA states on its website, "[h]ealth care providers with prescribing privileges (e.g., physicians, physician's assistants, nurse practitioners, or other health care providers) play a key role in

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[347] *Id.*

[348] *See Opioid Analgesic REMS Patient Counseling Guide*, available at https://opioidanalgesicrems.com/RpcUI/rems/pdf/resources/patient_counseling_document.pdf.

[349] *Id.*

ensuring that products with serious risks requiring REMS are prescribed and used safely."[350] Similarly, when the FDA received stakeholder comments in response to the proposed REMS, one main area of comments was that "[p]atient education is vital to the safe use of REMS drugs."[351] The FDA-approved Blueprint also states that "[w]hen HCPs have information about the risks of opioid misuse and abuse, they will be better able to create opportunities for patient counseling and other strategies to reduce these risks."[352] As for patients, several components of the REMS reflect the role that they play. Most notably, both the PCD and the Medication Guide are specifically intended for patients.

Third, the FDA's proactive approach to the REMS tellingly reflects its focus on guarding against the well-known risks of opioid medications—but nonetheless ensuring that patients who need them still have access to these important medicines. For example, the FDA noted in its February 2009 letter announcing the REMS as to Kadian® that the elements to assure safe use "must . . . not be unduly burdensome on patient access to the drug."[353] Similarly, as the FDA-approved Blueprint points it, the "FDA Blueprint was developed with two, competing, U.S. public health concerns in mind," one of which was the "epidemic of prescription opioid abuse" but the other of which was "the large number

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[350] *See* FDA Webpage re *Roles of Different Participants in REMS*, available at https://www.fda.gov/Drugs/DrugSafety/REMS/ucm592662.htm.

[351] *See* FDA Presentation on *Development of the 2012 Extended Release and Long-Acting (ER/LA) Opioid Analgesic REMS*, available at https://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM539363.pdf, at 7 (also noting that "[a] REMS that employs a patient registration system would be overly burdensome and create a stigma for pain patients that could adversely affect patient access to necessary medications").

[352] *See FDA Education Blueprint for Health Care Providers Involved in the Treatment and Monitoring of Patients with Pain* (September 2018), available at https://www.accessdata.fda.gov/drugsatfda_docs/rems/Opioid_analgesic_2018_09_18_FDA_Blueprint.pdf.

[353] February 6, 2009 FDA Letter, ALLERGAN_MDL_01774195.

of Americans with acute and chronic pain."[354] More fundamentally, the REMS itself is designed, as noted above, to ensure that the benefits of the medications continue to outweigh the risk; if the FDA did not believe that the benefits did not outweigh the risks, it would have not required a REMS but rather required the withdrawal of the medications from the market altogether.

C. The REMS was recently expanded to include immediate release opioids, including Norco®.

As approved in 2012, the REMS included only ER/LA opioids, like Kadian®, but not immediate release ("IR") opioids, like Norco®. In September 2017, the FDA announced that IR opioids intended for use in outpatient settings would be subject to the same REMS requirements as ER/LA opioids. Among the IR opioids that would be included was Norco®. On September 18, 2018, both Norco ANDAs were added to the REMS.[355] So too were several hundred other IR opioids.[356] On that same date, the name of the REMS was changed to "Opioid Analgesic REMS" in conjunction with the medication to the REMS.[357]

Norco®'s Medication Guide, one of the REMS elements, contains a host of plainly stated risk warnings.[358] For example, it says that Norco® is "[a]n opioid pain medicine

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[354] *See FDA Education Blueprint for Health Care Providers Involved in the Treatment and Monitoring of Patients with Pain* (September 2018), available at https://www.accessdata.fda.gov/drugsatfda_docs/rems/Opioid_analgesic_2018_09_18_FDA_Blueprint.pdf.

[355] FDA Webpage re *Opioid Analgesic REMS*, available at https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=REMSDetails.page&REMS=17.

[356] *Id.*

[357] *See https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=REMSDetails.page&REMS=17*

[358] Norco® Medication Guide (revised June 2018), available at https://www.allergan.com/assets/pdf/norco_pi (pages 25 and 26).

that can put you at risk for overdose and death" and that "[e]ven if you take your dose correctly as prescribed you are at risk for opioid addiction, abuse, and misuse that can lead to death."[359] Similarly, it states "[w]hen you first start taking NORCO® when your dose is changed, or if you take too much (overdose), serious or life-threatening breathing problems that can lead to death may occur."[360] These and other statements are written in plain, easy-to-understand language appropriate for the layperson.

XI. RESPONSE TO DR. KESSLER'S REPORT

A. Dr. Kessler's opinions regarding the promotion of Kadian® are flawed and inaccurate.

I have analyzed Dr. Kessler's opinions regarding the limited promotion of Kadian® by a former affiliate of Allergan,[361] which he refers to as "Actavis."[362]

First, below I explain the regulatory scheme and the FDA's role in enforcing the regulation of pharmaceutical promotional activities, which Dr. Kessler largely ignores. *Second*, I respond to Dr. Kessler's opinions regarding Actavis's promotional and training activities.

1. Dr. Kessler ignores the substantial role that the FDA plays in the regulation of marketing and promotion, including that materials are submitted to the FDA prior to their use.

The Center for Drug Evaluation and Research ("CDER") is the regulatory branch of the FDA tasked with regulating pharmaceutical marketing activities. The department within CDER tasked specifically with overseeing pharmaceutical advertising and promotion is the Office of Prescription Drug Promotion ("OPDP"), formerly known as the

[359] *Id.*
[360] *Id.*
[361] *See* Expert Report of David Kessler, M.D. (March 26, 2019) ("Kessler Report") at ¶¶ 494-537.
[362] Throughout this section, I adopt Dr. Kessler's convention of referring to the former Allergan affiliate involved with promoting Kadian® at the time as "Actavis."

Division of Drug Marketing Advertising and Communications ("DDMAC"). OPDP's mission is "[t]o protect the public health by assuring prescription drug information is truthful, balanced and accurately communicated," which "is accomplished through a comprehensive surveillance, enforcement and education program, and by fostering better communication of labeling and promotional information to both healthcare professionals and consumers."[363]

OPDP reviewers engage in a variety of tasks, including providing advisory guidance on proposed promotional materials; reviewing complaints about alleged promotional violations; initiating enforcement actions on false or misleading promotional materials; comparing promotional materials to the promoted medication's PI to determine consistency; traveling to major medical meetings and pharmaceutical conventions to monitor promotional exhibits and activities; and serving as liaison between OPDP and other divisions within the FDA on promotional matters.[364]

OPDP's authority to regulate pharmaceutical promotional activities is granted implicitly as a result of the Federal Food, Drug, and Cosmetic Act's prohibition of "misbranding." Specifically, the Act provides that "[a] drug or devise shall be deemed to be misbranded … [i]f its labeling is false or misleading in any particular."[365] The FDA has taken the position that this language in the Act gives it broad power to regulate the promotion of prescription pharmaceuticals.

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[363] The Office of Prescription Drug Promotion (OPDP), *available at* https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm090142.htm

[364] *Id.*

[365] 21 U.S.C. § 352(a).

Acting under this authority, the FDA has promulgated, and it enforces, specific and exacting regulations for advertising prescription pharmaceuticals.[366] These regulations cover everything from the proper description of drug ingredients[367] to the permissible size of letters that manufacturers can use in advertisements.[368] The regulations also cover the content of advertisements. For example, pharmaceutical advertisements must present a "true statement of information in brief summary relating to side effects, contraindications . . . and effectiveness."[369] Advertising claims are not considered true statements when (i) they are "false or misleading with respect to describing side effects, contraindications, or effectiveness,"[370] (i) they do not provide "fair balance" between effectiveness claims as compared to the side-effect and contraindications information,[371] or (iii) they do not include material side-effect information.[372]

Regarding the "fair balance" requirement, OPDP considers whether the "information relating to effectiveness is presented in greater scope, depth, or detail" than is required under the Federal Food, Drug, and Cosmetic Act, and whether "the presentation of true information relating to side effects and contraindications is comparable in depth and detail with the claims for effectiveness or safety."[373] That said, "no advertisement shall be considered to be in violation of this section if the presentation of true information relating to side effects and contraindications is comparable in depth and detail with the claims for

[366] 21 C.F.R. § 202.1.
[367] *Id*. at § 202.1(a)(1).
[368] *Id*. at § 202.1(b)(2).
[369] *Id*. at § 202.1(e)(1).
[370] *Id*. at § 202.1(e)(5)(i).
[371] *Id*. at § 202.1(e)(5)(ii).
[372] *Id*. at § 202.1(e)(5)(iii).
[373] *Id*. at § 202.1(e)(5)(ii).

effectiveness or safety."[374] Advertisements need not disclose *all* known side effects and contraindications. Such disclosures instead "may be limited to those pertinent to the indications for which the drug is recommended or suggested in the advertisement."[375]

Certain types of advertisements, like "reminder advertisements," are exempt from these requirements. "Reminder advertisements are those which call attention to the name of the drug product but do not include indications or dosage recommendations for use of the drug product."[376] Reminder advertisements need not comply with most of § 202.1; they must, however, contain the proprietary and established names for the medication, and may contain information concerning the manufacturer of the product, price of the product, and dosage form for the product.[377] This generally is not so when a medication's label "contains a boxed warning relating to a serious hazard associated with the use of the drug product," in which case the advertisement must comply with § 202.1; however, even for these products, a manufacturer may issue a reminder advertisement free from § 202.1's requirements when the "only purpose of the reminder advertisement … is to provide consumers with information concerning the price charged for a prescription for a particular drug product," and the advertisement "contains no representation or suggestion concerning the drug product's safety, effectiveness, or indications for use."[378] Such advertisements may include other information only if that information is neither false or misleading.[379] When the § 202.1 regulations do apply, OPDP considers them in its review of pharmaceutical marketing materials.

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[374] *Id*.
[375] *Id*. at § 202.1(e)(3)(iii)(a).
[376] *Id*. at § 202.1(e)(2)(i).
[377] *Id*.
[378] 21 C.F.R. § 200.200(a)(1); *see* 21 C.F.R. § 202.1(e)(2)(i).
[379] 21 C.F.R. § 200.200(a)(3).

Critically, pharmaceutical manufacturers commonly submit, to the extent required, their materials to OPDP "at the time of initial dissemination of the labeling and at the time of initial publication of the advertisement for a prescription drug product."[380] Before a manufacturer launches a new medication, if the manufacturer wishes to advertise it, it must submit its draft promotional materials to OPDP for approval. OPDP reviews these materials and provides commentary with revisions. The medication's sponsor then may respond, or may revise the materials for further review and signoff.

After this initial-review process, manufacturers resubmit, to the extent required, its advertising materials if it makes any changes in the materials—even stylistic changes or changes not affecting the content of the advertisement at all. Each such submission must be transmitted on Form 2253, and must include a copy of the medicine's current labeling.[381] This does not mean that OPDP must *expressly* approve of the material prior to publication or use.[382] Instead, OPDP must be afforded the opportunity to review. It its review, OPDP considers the promotional materials to ensure that they (1) are consistent with the product's package insert, (2) contain fair balance, and (3) are not misleading.[383]

OPDP reviews not only these submitted advertisements but rather also conducts its own monitoring, including by attending medical meetings and pharmaceutical conventions.[384] OPDP also may learn of improper advertisements from other medicine manufacturers, consumer protection groups, physicians, pharmacists, or patients. To that

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[380] 21 C.F.R. § 314.81(b)(3)(i).
[381] *Id*.
[382] *See* 21 C.F.R. § 202.1(j)(1).
[383] *Id*. at § 202.1(e)(5).
[384] The Office of Prescription Drug Promotion (OPDP), *available at* https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm090142.htm

end, OPDP runs a program called "Bad Ad" to encourage healthcare providers to inform OPDP of improper advertisements.[385]

In its review, if OPDP determines that a promotional material does not comply with the requirements above, it may take action against the medication's sponsor, including not only merely issuing a warning letter but also pursuing injunctions and consent decrees, referring the matter for criminal investigation or prosecution, and seizing problematic promotional materials, where appropriate.

To the extent that Dr. Kessler intends to suggest that FDA lacks the initiative or the resources to review and act on promotional material it receives when it has concerns, I disagree.

2. Actavis's limited promotion of Kadian® was appropriate from a regulatory perspective.

Dr. Kessler's opinions with respect to Actavis's limited promotion of Kadian®[386] are inaccurate, incomplete and otherwise flawed.[387] Below, I address each of the claims he makes, and evaluate promotional pieces and training materials he cites. As an initial matter, though, I offer a number of general observations about this section of Dr. Kessler's report.

First, Dr. Kessler sets out only a handful of Actavis marketing and training materials as examples for his broad conclusions. Even from those, he relies on short

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[385] Truthful Prescription Drug Advertising and Promotion, *available at* https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/DrugMarketingAdvertisingandCommunications/ucm209384.htm

[386] Dr. Kessler does not opine, or set out any evidence, that either Allergan or any current or former affiliate improperly promoted Norco® or any other opioid pain medication. *See generally* Kessler Report. Were there any such evidence, there is no doubt that Dr. Kessler would have set it out in the body of his 320-page, 681-paragraph report, or in one of its 12 schedules, which themselves span 516 pages.

[387] *See* Kessler Report at ¶¶ 494-537.

snippets of longer pieces—some numbering in the hundreds of pages—in an out-of-context attempt to foster the misimpression that the marketing was inappropriate. This suggests that Dr. Kessler was not evaluating Actavis's promotional activities from a fair perspective in order to present a balanced point of view but rather cherry-picking examples and stripping them out of context in an attempt to support pre-determined conclusions that Actavis's activities were inappropriate. *Second*, while Dr. Kessler purports to set out inappropriate marketing, neither he nor, to my understanding, any other of Plaintiffs' retained experts identify a single physician or other prescriber who was ever subjected to any of this marketing, much less a prescriber from or whose conduct affected either of Cuyahoga or Summit Counties. This is unsurprising, given that these materials were actually used by a very small salesforce for only a very limited amount of time—no longer than approximately mid-2009 to the February 2010 warning letter, after which they were immediately removed from circulation. As these facts do not first Dr. Kessler's opinions, he has omitted them. *Third*, Dr. Kessler did not identify a single prescription written as a result of any of the Actavis marketing, much less one in or affecting Cuyahoga or Summit Counties. *Fourth*, Dr. Kessler ignores that any hypothetical doctors who he suggests could have been confused by Actavis's pre-warning letter marketing would have shortly thereafter become "unconfused" by the corrective action.

The February 18, 2010 FDA warning letter and referenced materials. Dr. Kessler's report relies heavily on a warning letter to Actavis from the FDA dated February 18, 2010.[388] These opinions are flawed and paint an incomplete picture of the facts. In

[388] *See, e.g.*, Kessler Report at ¶¶ 500-504, 505.2, 507-509, 511-519.

addition to several others set out above (*see* § VIII), I offer several observations in response to Dr. Kessler.

First, Dr. Kessler merely largely parrots what is stated in the FDA warning letter without providing any analysis of its validity. Dr. Kessler offers no facts in support. I have set out my substantive evaluation of the letter and referenced materials above. *See supra* § VIII.

Second, Dr. Kessler fails to mention that the promotional materials that were the subject of the warning letter had been submitted to the FDA for review under cover of Form 2253 months ahead of time.[389] The Co-Pay Brochure was submitted on February 16, 2009 (more than a year before the letter) and the Comparison Detailer on June 24, 2009 (more than seven months before the letter). *See supra* § VIII.

Third, Dr. Kessler ignores that the FDA took no further action against Actavis in the wake of the warning letter but rather expressed full satisfaction[390] at its corrective action plan. I too have evaluated Actavis's corrective active program in detail and have concluded that Actavis's actions were conservative and responsible—especially given that Actavis could have chosen to contest the FDA's stated concerns. *See supra* § VIII. Dr. Kessler, in contrast, simply ignores Actavis's corrective action program.

Fourth, Dr. Kessler ignores that, to the extent there were any misapprehensions left by the marketing that was the subject of the warning letter, they were fully corrected by the corrective action plan. *See supra* § VIII.

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[389] *See* 21 C.F.R. § 314.81(b)(3).

[390] *E.g.*, August 4, 2010 Letter from FDA, ALLERGAN_MDL_01238281 at 2 ("DDMAC has determined that the revised dissemination plan and Dear Consumer and DHP letters adequately address the issues raised in the Warning Letter and have no further comments at this time.").

Post-warning letter training and background materials. Dr. Kessler also wrongly criticizes a number of Actavis's training materials.

As an initial matter, these training and background materials, by definition, were not provided to physicians or other prescribers. Some, like the Kadian Learning System, were mere background reading for sales representatives.[391] The Kadian Learning System even states, on every page, that it was "For Internal and Training Purposes ***Only***" and "***Not*** to be Distributed."[392] As noted above, Dr. Kessler does not point to any prescriber or physician in Cuyahoga or Summit Counties to whom any of the content in the training or background materials was communicated.

Dr. Kessler is also wrong on the substance of these materials. For example, referencing the 2010 version of the Kadian Learning System, and in support of his misguided opinion that "[d]espite FDA's warning that Actavis should refrain from marketing Kadian for use in broader populations than indicated, Actavis used promotional messages similar to those describes," Dr. Kessler writes that "Actavis's sales training for Kadian included a general and expansive definition of pain that was not focused on the 'moderate to severe' pain threshold that Kadian was intended to treat."[393] But the page of the Kadian Learning System that Dr. Kessler cites merely contains basic information on pain, defining what it is generally; it is silent on the types of pain for which Kadian® is indicated.[394] It does not even purport to define Kadian®'s indication, or to suggest in any

[391] 2010 Kadian Learning System, ALLERGAN_MDL_01610522.
[392] *Id.* (emphasis added).
[393] Kessler Report at ¶¶ 505-505.1 (citing 2010 Kadian Learning System, ALLERGAN_MDL_01610522).
[394] 2010 Kadian Learning System, ALLERGAN_MDL_01610522 at ALLERGAN_MDL_01610529.

way or by any stretch that Kadian® be prescribed for pain for which it was not indicated.[395] Elsewhere, the Kadian Learning System correctly states that "KADIAN is intended for use in patients with moderate or severe pain who require more than several days continuous treatment with a potent opioid analgesic," in accordance with Kadian®'s then-current indication in its FDA-approved labeling.[396]

Similarly, Dr. Kessler states that "Kadian sales representatives were trained that Kadian users who were 'pseudoaddicted' could be differentiated from individuals with 'physical dependence,' 'tolerance,' and 'addiction.'"[397] His cited support for that idea is a quote from a different version of the Kadian Learning System: "The problem is even more complex because some patients who are undertreated for their physical pain show the symptoms of 'pseudoaddiction.'" Pseudoaddiction is a set of behaviors (Table 1-3) that are exhibited by patients with inadequately treated pain, including patients with cancer pain. Pseudoaddictive behaviors are not signs of substance abuse, but rather should be considered symptoms of inadequate treatment."[398] He ignores, though, that immediately preceding that quote is the clear statement that "some chronic pain patients do have a substance abuse problem (Table 1-2)."[399] In turn, Table 1-2 sets out a corresponding list of "Signs Associated with Substance Abuse"—not pseudoaddiction.[400]

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[395] *Id.*
[396] *Id.* at ALLERGAN_MDL_01610701.
[397] Kessler Report at ¶ 536 & n.1095
[398] *Id.* (citing ALLERGAN_MDL_00439499).
[399] ALLERGAN_MDL_00439499 at p. 22.
[400] *Id.* at p. 21.

Likewise, Dr. Kessler criticizes three statements from a September 2012 training presentation.[401] Dr. Kessler, though, omits that the presentation cites clinical support for all three of these statements.[402]

In addition, Dr. Kessler cites and quotes from two draft versions of the same presentation. First, Dr. Kessler cites what he refers to as a "February 2013 Kadian Sales Training Presentation," which he says stated that "Kadian provides steady blood levels of morphine sulfate with few peaks and valleys."[403] This, though, is a draft presentation dated *after* Actavis ceased in-person detailing for Kadian®.[404] That this was a draft is clear from its face. One slide merely states, for example, "Insert picture of Dosing Guide."[405] Another slide states: "Pain slides - insert summary slides from Marianne's deck."[406] Dr. Kessler's use of this document is emblematic of his stretching to find evidence that Actavis engaged in the conduct he assumes it did. Second, Dr. Kessler cites from a March 2013 draft of the same presentation.[407] That this document is a draft is clear from its face, as it reflects numerous handwritten edits.[408] In fact, a portion of the very statement that Dr. Kessler quotes is crossed out in the draft:

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[401] *See* Kessler Report at ¶ 519 n.1063 (citing ALLERGAN_MDL_00020454). The three statements are: (i) "KADIAN patients experience sustained morphine release with less fluctuations vs. morphine sulfate"; (ii) "KADIAN patients report improved management of pain vs. morphine sulfate"; and (iii) KADIAN patients require less rescue medication vs. morphine sulfate." *Id.*

[402] ALLERGAN_MDL_00020454 at pp. 17 (citing NDA study MOB-1/90 plus medical publication), 21 (citing medical publication), 24 (citing medical publication).

[403] Kessler Report at ¶ 389.3 & n.1065. Although Dr. Kessler's report numbers this paragraph as 389.3, it appears directly below paragraph 520.

[404] ALLERGAN_MDL_00001525.

[405] *Id.* at ALLERGAN_MDL_00001554.

[406] *Id.* at ALLERGAN_MDL_00001527.

[407] Kessler Report at ¶ 389.2 & n.1065 (quoting from ACTAVIS0000564). This paragraph also appears directly below paragraph 520 of Dr. Kessler's Report.

[408] *See* Draft March 2013 "Sales Training Presentation," ACTAVIS0000564.

Kessler Report[409]

389.2 March 2013 marketing sales training presentation instructed:

"Kadian provides steady blood levels with few peaks and valleys (show PK charts from Detail Aid)"[1065]

Source Document[410]

once-a-day administration of KADIAN®.

Remove "with few peaks and valleys"

KADIAN® provides steady blood levels of morphine sulfate with ~~few peaks and valleys.~~

Regardless, as is clear from the fact that he relies on two different draft versions of the same document, Dr. Kessler offers no evidence that this presentation was used to train sales representatives—much less that any statements from it reached any prescriber in or affecting Cuyahoga or Summit Counties.

Dr. Kessler also ignores these training and background materials' robust, plainly-stated risk warnings. The Kadian Learning System, for instance, contains (among many other risk disclosures) a list of "FDA Safety Warnings" straight from the PI's boxed warning, such as "KADIAN® contains morphine sulfate, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics," and "KADIAN® can be abused in a manner similar to other opioid agonists, legal or illicit."[411] Similarly, it includes other warnings included in the FDA-approved PI, such as

[409] Kessler Report at ¶ 389.2.

[410] *See* Draft March 2013 "Sales Training Presentation," ACTAVIS0000564 at ACTAVIS0000590; *see also id.* at ACTAVIS000593 (same handwritten correction to statement also cited by Dr. Kessler). Separately, Dr. Kessler added the words "(show PK charts from Detail Aid)," which also do not appear in the document. Kessler Report at ¶ 389.2.

[411] *Id.* at ALLERGAN_MDL_01610685-86.

"KADIAN® may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression because respiratory depression, hypotension, and profound sedation or coma may result."[412]

Reports regarding Kadian®'s abuse potential. Dr. Kessler opines that "Actavis received reports that the message that Kadian had 'low abuse potential' was delivered to prescribers."[413] This is misleading, because it implies that Actavis promoted Kadian® as having "low abuse potential"—despite that he cites not a single marketing piece, training material or other evidentiary support evidencing that Actavis made any such statements (much less, of course, to any Cuyahoga or Summit County prescriber).

Rather than set out any such evidence, Dr. Kessler relies on the results of a marketing survey performed by a third party in 2011.[414] The survey took into account only 12 prescribers.[415] More to the point, the survey did not purport to reflect what Actavis had communicated to even these prescribers (to the extent it had marketed to them at all); rather, it simply reflected certain prescribers' beliefs.[416]

This opinion by Dr. Kessler illustrates more broadly the most fundamental flaw in his opinions about Actavis: Because he has no adequate evidence to support his opinions as to Actavis, he takes statements out of context and implies that they suggest wrongdoing that did not occur.

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[412] *Id.*
[413] *See* Kessler Report at ¶ 521.
[414] *See id.* (citing ACTAVIS0268659 and ALLERGAN_MDL_00072907).
[415] *See* ACTAVIS0268659 at slide 2 ("Research Methodology and Objectives").
[416] *See generally id.*

Journal of Pain study. Dr. Kessler also wrongly opines that "Actavis misleadingly promoted Kadian as having no alcohol-induced dose dumping effect" based on Actavis's distribution of a published article in the Journal of Pain.[417]

As an initial matter, the article was not "supported" by Actavis in 2007, as Dr. Kessler claims.[418] Rather, as the face of the article demonstrates, it was Alpharma—not Actavis—that was involved with the research.[419] This study occurred in 2007, before Actavis acquired Kadian®.

Regardless, I see no issue from a regulatory perspective with Actavis's use of this article, as such use of research articles is explicitly permitted, including their distribution.[420] To the extent Dr. Kessler implies that 21 U.S.C. § 355(d) prohibits the dissemination of medical research that does not consist of "two, adequate and well-controlled trials,"[421] I am not not aware of any such authority supporting that view, and Dr. Kessler has not set out any.

Indeed, Alpharma performed this study on the FDA's recommendation.[422] The article even states that "[t]he FDA has reviewed data from this study" and "has concurred that there is no interaction between KADIAN and alcohol in vivo when administered concomitantly, and has not required any changes to the package insert."[423] In other words, the FDA not only recommended this study but reviewed data, concurred with its results,

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[417] Kessler Report at ¶¶ 523-533.
[418] *Id.* at ¶ 523.
[419] ALLERGAN_MDL_01741520 at ALLERGAN_MDL_01741520 (referring to "Alpharma Pharmaceuticals LLC").
[420] *Guidance for Industry Distributing Scientific and Medical Publications on Risk Information for Approved Prescription Drugs and Biological Products—Recommended Practices* (June 2014), available at https://www.fda.gov/media/88674/download.
[421] *See* Kessler Report at ¶ 526.
[422] Kessler Report at ¶ 524.
[423] ALLERGAN_MDL_01741520 at ALLERGAN_MDL_01741525.

and declined to require any changes to the PI. This is supported by a February 27, 2007 letter from the FDA to Alpharma (who then owned Kadian®) stating that "[s]upplemental new drug application 021 provides for changes to the package insert to include information about the *in vitro* finding that the extended-release characteristics of Kadian are compromised in the presence of alcohol and warnings about the potential for dose dumping *in vivo* if Kadian is taken concomitantly with alcohol" but that "due to your *in vivo* data demonstrating that there is not an interaction between Kadian and alcohol *in vivo* when administered concomitantly, the changes originally proposed in S-021 are no necessary."[424] Especially in light the FDA's review and approval of this Alpharma study, as well as its decision to make the Kadian® PI consistent with the results of the study, Dr. Kessler's suggestion that it was in any way inappropriate for Actavis to distribute this article is groundless.

In addition, Actavis provided its sales force clear, appropriate guidance on the distribution of this article.[425] A training presentation on the article states, for example, that detailers should "discuss safety considerations with prescribers during each call."[426] And, contrary to Dr. Kessler's opinion that "Actavis Misleadingly Promoted Kadian as Having No Alcohol-Induced Dose Dumping Effect," this training establishes exactly the opposite. It instructs that "[w]hen discussing the effect of alcohol on KADIAN, main message must be" that "[t]he co-ingestion of alcohol with KADIAN capsules is not recommended" and that "[a]ll opioids, including KADIAN capsules, may be expected to have addictive effects

[424] ALLERGAN_MDL_03877541 at ALLERGAN_MDL_03877541.
[425] *See* November 2009 *KADIAN® Sales Team Training for Use of the Reprint*, ALLERGAN_MDL_00438611.
[426] *Id.* at slide 11.

and potentially serious outcomes when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression."[427] Actavis also instructed sales people to "[d]iscuss the importance/seriousness of this issue," including that "[s]tatistics suggest most adults ingest alcohol" and that "[d]ose-dumping can be fatal."[428] And Actavis required its sales force to include a copy of the FDA-approved PI whenever distributing the article.[429] The "Perspective" at the beginning of the piece also states that "[b]ecause of the high rate of alcohol use in the United States, the potential for drug-alcohol interactions is an important clinical concern" and that although "results of this *in vivo* study indicate that the risk of alcohol-induced dose-dumping in connection with the use of KADIAN is negligible," "it is recommended that alcohol not be used while the patient is taking opioids."[430]

In any case, Dr. Kessler ignores that Actavis distributed this article for fewer than five months, no earlier than October 2009 and no later than February 2010.[431] And, again, Dr. Kessler fails to identify a single prescriber in Cuyahoga or Summit Counties who received this article, much less one who wrote a prescription that should not have been written as a result of it.

Alpharma materials. Dr. Kessler relies on a document regarding not Actavis but rather Kadian®'s former owner, Alpharma, as the sole support for several of his opinions about Actavis. For example, he writes: "Actavis recognized that 'the market for both acute

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[427] *Id.*
[428] *Id.*
[429] *Id.* ("Distribution of the reprint must include a copy of the package insert.").
[430] ALLERGAN_MDL_01741520 at ALLERGAN_MDL_01741520.
[431] *See* October 15, 2009 N. Leitch Email, ALLERGAN_MDL_01741504 (indicating that Actavis had not yet started using the article); Kessler Report at ¶ 530 (indicating that "Actavis stopped using the alcohol study" no later than 2010).

and chronic pain medications [was] increasing, [and] that the chronic pain segment had experienced [] dramatic growth."[432] He also writes: "The Kadian marketing plan took into account that 'over half of the people taking prescription or over-the-counter drugs [were] NOT satisfied with their current treatment plan,' and that this presented 'a significant marketing opportunity for the right drug in the chronic pain market.'"[433] In both cases, Dr. Kessler cites only a single document: a 2005 *Alpharma* document.[434] This document has no bearing on Actavis's conduct, which Dr. Kessler knows given his express acknowledgement that Actavis purchased Kadian® from Alpharma only years later.[435] Dr. Kessler's use of this non-Actavis document wholly undermines each of Dr. Kessler's opinions supported by it, as they are left with no other evidentiary support.

Materials that Dr. Kessler did *not* reference. As noted, Dr. Kessler paints an incomplete picture of the brief period—approximately mid-2009 to late 2012—when Actavis (via a modest contract sales force from inVentiv) detailed Kadian® to prescribers in-person. To create this false impression, Dr. Kessler presents a one-sided view of small portions of a handful of documents. In doing so, Dr. Kessler wholly ignores other Kadian® promotional materials, particularly those from after the FDA's warning letter.

I have reviewed a number of these marketing materials for Kadian®, analyzing them from a regulatory perspective. As a general matter, I found them all to be very conservative and appropriate. Notably, they were tightly tied to Kadian®'s FDA-approved

[432] Kessler Report at ¶ 497.
[433] *Id.* at ¶ 498.
[434] *Id.* at ¶¶ 497-498 & n. 1038-1039 (citing ACTAVIS00006930).
[435] *Id.* at ¶ 494 n.1035.

PI. With respect to each piece, I concluded that they were appropriate from a regulatory perspective.

For example, I reviewed a Co-Pay card.[436] Consistent with the applicable regulations, the Co-Pay card's sole purpose was "to provide consumers with information concerning the price charged" for the drug, and the card "contain[ed] no representation or suggestion concerning the drug product's safety, effectiveness, or indications for use."[437] True enough, there is additional information concerning the Co-Pay program—for example, it states there is "[n]o expiration date" for the card and "[n]o upfront patient cost," and the card contains instructions for redemption[438]—but this information is permissible because it is not false or misleading, and does not concern Kadian®'s safety, effectiveness, or indications.[439] Moreover, the card goes above and beyond what is required by instructing consumers to "[p]lease read accompanying Full Prescribing Information";[440] such language is not required for reminder advertisements.

A Co-Pay Assistance Program brochure I reviewed is also appropriate from a regulatory perspective.[441] The brochure is a total of seven pages, with a frequently asked questions section up front. Like the card, the brochure contains pricing information and instructions for participating in the Co-Pay program on the FAQ page and the first page.[442] The rest of the piece contains the PI, the Kadian® indication, and the boxed warning for Kadian® prominently displayed on the second page.[443] In addition, each page instructs the

[436] ALLERGAN_MDL_00992370.
[437] 21 C.F.R. § 200.200(a)(1); *see* 21 C.F.R. § 202.1(e)(2)(i).
[438] ALLERGAN_MDL_00992370.
[439] 21 C.F.R. § 200.200(a)(3).
[440] ALLERGAN_MDL_00992370.
[441] ALLERGAN_MDL_00992372.
[442] ALLERGAN_MDL_00992372.
[443] *Id*.

consumer to "[p]lease see [the] Boxed WARNING on page 2, Important Safety Information on pages 3-7, and accompanying Full Prescribing Information and Medication Guide."[444] In my opinion, the totality of this piece easily meets the fair balance standard, as most of it is comprised of FDA-approved labeling information.

As another example, I also reviewed a Kadian® detail aid.[445] A detail aid is a "brochure that [sales] representatives use to educate physicians when they're in their office."[446] The front page of the detail aid contains an announcement for four new strengths of Kadian®—40 mg, 70 mg, 130 mg, and 150 mg.[447] The next three pages contain the boxed warning, Kadian® indication, and important safety and risk information; the final page again contains the Kadian® boxed warning.[448] The remaining pages present scientific information about blood plasma levels with Kadian®, information about the Kadian® capsule, metabolic information about Kadian®, and dosing and administration information; there is also fair balance, as risk and safety information is imbedded throughout these pages.[449] None of these are comparative claims. Finally, each page contains the same warning as in the Co-Pay Assistance Program brochure, instructing the viewer to review the boxed warning, important safety information, and accompanying full prescribing information and medication guide.[450] Like the Co-Pay Assistance Program brochure, the detail aid is based on and created from the Kadian® prescribing information, which of course was approved by the FDA.[451]

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[444] *Id*.
[445] ALLERGAN_MDL_01215562.
[446] *See* J. Altier Dep. Tr. at 76:17–20.
[447] ALLERGAN_MDL_01215562,
[448] *Id*. at -63–64, -68.
[449] *Id*. at -64–68.
[450] *Id*.
[451] *See* J. Altier Dep. at 220:1–222:19.

In addition, I reviewed a Kadian® conversion guide.[452] A conversion guide is a marketing piece containing information from third-party sources showing equivalencies between various medicines—for example, the relative potency of morphine versus other products.[453] Physicians use this piece if they determine that it is appropriate to switch their patients from various medicines to Kadian®.[454] The first page of this guide with substantive information warns prescribers that "[t]here is a lack of systematic evidence about these types of analgesic substitutions," and thus, "specific recommendations are not possible"; however, physicians must exercise their medical judgment to "determine and adjust the actual dose of Kadian® on a patient-specific basis."[455] The next several pages provide the Kadian® boxed warning, indication, and important safety and risk information; the final page again presents the Kadian® boxed warning.[456] On the second-to-last page, there is a reserved space indicating that the Kadian® PI was to be inserted in full.[457] The remainder of the piece contains administration information, information about the Kadian® capsule, metabolic information, and information for converting a patient from other types of opioids (*e.g.*, fentanyl, hydrocodone, oxycodone) to Kadian®; as with the Detail Aid, risk and safety information is embedded throughout these pages.[458] Notably, nothing in the Conversion Guide instructs or recommends that prescribers switch their patients from other opioids to Kadian®; instead, this guide serves as a tool for a prescriber to switch his patients if he or she determines a switch to be appropriate in his professional medical

[452] ALLERGAN_MDL_00007569.
[453] *See* N. Leitch Dep. at 128:15–23.
[454] *See* J. Altier Dep. at 77:1–6.
[455] ALLERGAN_MDL_00007569, at -70
[456] *Id*. at -71–77, -03–06.
[457] *Id*. at -05.
[458] *Id*. at -77–01

judgment. Finally, as in the Co-Pay Assistance Program brochure and Detail Aid, the Conversion Guide routinely instructs the viewer to review the boxed warning, important safety information, and accompanying full prescribing information and medication guide.[459]

I also reviewed a Kadian® dosing guide.[460] The dosing guide is very similar to the other pieces I reviewed. Like the other materials, the dosing guide begins with the boxed warning, Kadian® indication, and important safety and risk information.[461] The balance of the piece contains dosing and administration information, information about the Kadian® capsule, and metabolic information, with safety and risk information imbedded throughout.[462] Finally, like the other marketing pieces, the Dosing Guide routinely instructs the viewer to review the boxed warning, important safety information, and accompanying full prescribing information and medication guide.[463] This piece too contains ample fair balance, with robust risk disclosures.

In sum, review of Kadian® marketing materials beyond those set out in Dr. Kessler's report reveals that Actavis's limited promotional activities were appropriate from a regulatory perspective.

B. In playing up manufacturers' responsibilities under the Act, Dr. Kessler ignores the FDA's critical role.

As detailed above, I have explained the FDA's dominant role in enforcing the regulation of pharmaceutical promotional activities, which Dr. Kessler failed to articulate. Without so much as referencing the FDA's statutory obligation to enforce the provisions

[459] *Id*. at -69–06.
[460] ALLERGAN_MDL_00001236
[461] *Id*. at -37–39
[462] *Id*. at -40–43.
[463] *Id*. at -36–44.

on misbranding via false or misleading labeling obligations under Section 502 of the Act and its amendments, Dr. Kessler exaggerates the labeling and promotional responsibilities of drug manufactures. FDA's long and history of increasingly intensified opioid-related actions relating to the safety and effectiveness of opioids in general are well documented testimony to this reality. *See supra* § VII.

C. While Dr. Kessler attempts to implicate Actavis in his opinion that manufacturers meaningfully sponsored pain and other such organizations, he cites no evidence of such in connection with Kadian®.

Among Dr. Kessler's opinions is that "the opioid manufacturers' support for and involvement with pain advocacy, professional medical organizations, and trade group organizations, expanded the use of opioids and increased the risk of abuse."[464] Dr. Kessler fails to except Actavis or Allergan from that statement.

Yet, he makes only one reference in this entire section to either of Actavis or Allergan. Dr. Kessler writes: "APS [American Pain Society] maintained a 'Corporate Council' program that is sponsored by opioid manufacturers. . . . Members of APS's Corporate Council include Endo, ***Actavis***, Mallinckrodt, Purdue, and Janssen."[465] In support, Dr. Kessler cites only two documents.[466] One, a U.S. Senate report called "Fueling an Epidemic (Report Two)," which tellingly nowhere even mentions Actavis or Allergan.[467]

The second document Dr. Kessler cites far from establishes any substantial participation in any of these organizations in connection with Kadian®. It is a document produced by Teva that briefly mentions "Activis" as being in the "second tier" of

[464] *See* Kessler Report at § XI (p. 295).
[465] *Id.* at ¶ 583 & n.1164 (emphasis added).
[466] *Id.*
[467] *See Fueling an Epidemic (Report Two)*, https://www.hsdl.org/?abstract&did=808171.

sponsorship of APS's "Corporate Council."[468] Indeed, my review of the record indicates that Actavis joined APS's Corporate Council only briefly, in 2012.[469] In fact, a document itemizing payments and transfers purportedly received by APS shows only one from Actavis, in 2012, for $15,000.[470] Further, it did so not in connection with Kadian® but rather MoxDuo—an opioid medication whose NDA was sponsored by another, unaffiliated company that was never approved or sold.[471] This brief involvement in one of the organizations to which Dr. Kessler refers was hardly substantial or meaningful; he nowhere sets out any such evidence anywhere.

Thus, despite repeatedly referring to the "opioid manufacturers" throughout this section to suggest that *all* such companies were meaningfully involved in these organizations, Dr. Kessler does not set out any evidence that *Allergan's* "support for and involvement with pain advocacy, professional medical and trade groups," to the limited extent there was any such involvement, had any role in "expand[ing] the use of opioids" or "increased the risk of abuse," as Dr. Kessler opines. Nor am I aware of any such evidence.

XII. RESPONSE TO DR. EGILMAN'S REPORT

Dr. Egilman, another of Plaintiffs' proffered experts, sets out 489 separate statements that he labels "Opinions."[472] Of those, a number relate to the FDA and its regulations of opioid medications. I have evaluated these FDA-related statements to the

[468] *See* TEVA_MDL_A_00499668.
[469] *See, e.g.*, Ex. 4 to J. Barrett Deposition (April 2012 email "invit[ing] Actavis to join the APS Corporate Council").
[470] *See* APS_MDL00000001 at APS_MDL00000005.
[471] *See* Kessler Report at Schedule 7.
[472] *See* Report of David S. Egilman MD, MPH (March 25, 2019) ("Egilman Report").

extent they relate to Allergan, and I disagree with each of them. My responses to a number of these purported statement are set out below.

"**Opinion" 7.53.** Dr. Egilman states that "[t]he FDA agrees that there is insufficient evidence that the risk of opioids outweighs the benefits for treatment of chronic non-malignant pain."[473] This is incorrect, and it betrays a fundamental misunderstanding of the FDA's regulation of these medications. To the contrary, and as noted above, the FDA has required indications in the labeling for extended-release, long-acting opioids such as Kadian® that state that they are indicated for "the management of pain severe enough to require daily, around-the-clock, ***long-term*** opioid treatment and for which alternative options are inadequate."[474] To approve that indication, the FDA necessarily found that the benefits of opioid medications bearing it outweighed their risks when used in accordance with that indication, and were safe and effective for such use. For example, the extension studies mentioned above showed safety and no loss of effectiveness during long treatment periods, ranging from 12-52 weeks. *See supra* § V. Further, in response to the 2012 PROP Citizen Petition, the FDA stated that "[i]t is FDA's view that a patient without cancer, like a patient with cancer, may suffer from chronic pain, and PROP has not provided scientific support for why labeling should recommend different treatment for such patients," and it expressly "decline[d] to make a distinction between cancer and non-cancer chronic pain in opioid labeling." *See supra* § VII.C.

[473] Egilman Report at § 7.53; Egilman Exhibit B.53.

[474] Kadian PI (revised September 2018), available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/020616s061s062lbl.pdf (emphasis added).

The only source that Dr. Egilman cites in support of this statement is a February 25, 2019 Washington Post article, part of which he pasted directly into Exhibit B.53 to his report. But that the FDA may be requiring additional studies on the efficacy of certain opioid medications for certain uses does not support Dr. Egilman's point that the "FDA agrees that there is insufficient evidence that the risk of opioids outweighs the benefits for treatment of chronic non-malignant pain." Rather, it shows only the FDA's continued vigilance in not only responding to but working to develop additional research into the safety and efficacy of opioid pain medications.

"Opinion" 7.69. Dr. Egilman writes that "[t]he 'Venture' Corrupted the FDA."[475] As an initial matter, here and elsewhere Dr. Egilman states that the FDA does not operate independently from the companies it regulates, based on observing that some former FDA employees were subsequently employed by pharmaceutical companies. The strict conflict of interest rules of engagement of FDA with the companies that it regulates,[476] as well as post-FDA restrictions on employment with regulated industry,[477] render Dr. Egilman's insinuation untrue and without factual basis.

Dr. Egilman's sole support for "Opinion" 7.69 appears in Exhibit B.69, which merely contains a screen grab of an article about the approval of Zohydro ER, an opioid medication owned by a non-Defendant.[478] Nor does Dr. Egilman set out, here or

[475] Dr. Egilman separately defines "the 'Venture'" as "all Defendants in the Opiate Litigation (including their associated individuals and/or organizations) acting in a concerted fashion separately or together to effect a particular objective." *See* Egilman Report at § 4.4.

[476] *E.g.*, Prohibited Financial Interests for FDA Employees, available at https://www.fda.gov/about-fda/ethics/prohibited-financial-interests-fda-employees.

[477] *E.g.*, Post-Employment Restrictions, available at https://www.fda.gov/about-fda/ethics/post-employment-restrictions.

[478] Egilman Exhibit B.69.

elsewhere, any evidence that Allergan engaged in any conduct whatsoever that "corrupted the FDA."

"Opinion" 7.70. Dr. Egilman writes that the "FDA failed to properly regulate opioid indications" and that "when the FDA tried to limit use in 2001 by changing the label from 'more than a few days' to 'extended period of time', the 'Venture' used this language to increase the market."[479]

The statement that the "FDA failed to properly regulate opioid indications" is baseless. Dr. Egilman sets out no reasoning for it. As set out above (*e.g.*, §§ IV, VII, IX), the FDA has devoted enormous resources to regulating the FDA-approved labeling, including that for Kadian® and Norco®.

I have also evaluated the statement that "the 'Venture' used [certain labeling language] to increase the market" from Allergan's perspective. I have seen no evidence that Allergan improperly used any language in any label in any way. Indeed, Allergan (more specifically, a former affiliate) did not acquire Kadian® until December 2008. By this time, the "increase" to which Dr. Egilman is apparently referring would have long since occurred; it could not logically be attributable to Allergan's Kadian® promotion or other conduct.

Dr. Egilman's sole support for this statement is outlined in his Exhibit B.68, which is merely a list of Bates-numbered documents.[480] I have evaluated the documents produced by Allergan that appear on this exhibit. None supports Dr. Egilman's statement. Indeed, it is unclear why he cited them, which neither his report nor Exhibit B.68 explains. For

[479] Egilman Report at § 7.70.
[480] Egilman Exhibit B.68 and documents cited therein.

example, Dr. Egilman goes so far as to cite several documents that relate not to Allergan but to non-Defendant Alpharma—the prior owner of Kadian®.[481] Several others simply reflect Allergan training sales representatives, to the limited extent it used them, on the FDA-approved indications for Kadian®.[482] But the record of Allergan's training of its sales force on the FDA-approved labeling—including the many risk warnings—shows Allergan's diligence and responsibility. Training sales representatives on a medication's FDA-approved labeling certainly does not suggest misconduct, as Dr. Egilman implies.

"Opinion" 7.71. Dr. Egilman writes that "the 'Venture' used the revolving door FDA-industry to get favorable rulings to enable them to expand the market to patients who they and the FDA knew were inappropriate for long term narcotics."[483] I have seen no support that Allergan did any such thing. Indeed, Dr. Egilman's exhibit setting out the "[b]asis" for this statement includes no evidence related to Allergan at all.[484]

"**Opinion" 7.72.** Dr. Egilman writes that "[t]he head of the Division of the FDA responsible for opioids being approved is not a 'watchdog' to the American people."[485] This statement is without merit. To the extent he is referring to CDER, the part of the FDA that reviews NDAs, I served as Director of CDER from 1987 until 1993. I strongly disagree that either during that time period or since CDER has not served as a watchdog for protecting the American people.

Further, Dr. Egilman does not set out anything that supports this statement.[486] While he pastes in a news article about IMPACCT, an organization whose "stated goal is

[481] *E.g.*, ACTAVIS0006930; ALLERGAN_MDL_00814900.
[482] *E.g.*, ACTAVIS0197924 at slide 3.
[483] Egilman Report at § 7.71.
[484] Egilman Exhibit B.71.
[485] Egilman Report at § 7.72.
[486] Egilman Exhibit B.72.

to improve the design of clinical trials conducted to develop new pain treatments," the article he cites does not even mention any head of the CDER division that is responsible for opioid pain medications.[487] Nor have I seen any evidence that Allergan participated in IMPACCT with respect to or for the purpose of opioids, and Dr. Egilman sets out none.

"Opinion" 7.103. Dr. Egilman writes that "IMMPACT was 'Venture's' successful effort to have the FDA adopt poor epidemiologic practices to approve opioids" and that "it was pay to play and probably violated ant[i]-trust laws as well."[488] To the extent this statement is coherent, Dr. Egilman provides no support that Allergan caused the FDA to "adopt epidemiologic practices to approve opioids," that the FDA adopted "poor epidemiological pratices," participated in "pay to play," or "violated ant[i]-trust laws."[489] To the contrary, as I explain above, I have evaluated the FDA's review of approval of Kadian® and Norco®, both of the Allergan opioids at issue in this case, and I have seen nothing suggesting anything but the FDA's robust, appropriate consideration of those applications. *See supra* §§ V-VI. Further, both Kadian® and Norco® were approved and monitored for years before the alleged "successful effort," which Dr. Egilman wholly ignores. *See id.*

"Opinion" 7.195. Dr. Egilman writes: "Revolving door - Dr. Gottl[ie]b supports IMMPACT while investing in pharmaceutical companies and then becomes head of FDA."[490] This statement is unsupported except for a link to a New York Times article regarding former FDA Commissioner Dr. Scott Gottlieb, who served as Commissioner

[487] *Id.*
[488] Egilman Report at § 7.103.
[489] *See* Egilman Exhibit B.103.
[490] Egilman Report at § 7.195.

between May 2017 and April 2019.[491] The article does not suggest anything untoward between Dr. Gottlieb and Allergan and notes that, to the extent Dr. Gottlieb had relationships with pharmaceutical companies, he would recuse himself as appropriate.[492]

"**Opinion" 7.201.** Dr. Egilman states that "[t]he 'Venture' and FDA had off the record conversations to coordinate policy decisions" and that "Haddox represents 22 companies."[493] As an initial matter, Dr. Egilman does not specify to what "record" he is referring. It is not unusual, and it is entirely appropriate, for medication sponsors to communicate with the FDA in non-public fora. In fact, it is necessary to the proper functioning of the system. Nor do the two email chains that Dr. Egilman cites in support of this statement suggest any inappropriate conduct, much less any on Allergan's account.[494]

"Opinion" 7.349. Dr. Egilman writes that "the 'Venture' influenced the FDA Risk Evaluation and Mitigation Strategy (REMS) Program."[495] To the extent this statement makes sense, it is misguided. As set out above, Allergan and the other companies who have participated in the REMS were required to do so by the FDA, and their participation in the FDA-approved REMS was a positive feature. *See supra* § X.[496]

Further, while Dr. Egilman states in the exhibit supporting this statement that several companies (including "Allergan" as well as several Defendants and non-

[491] *See* Egilman Exhibit B.195 (citing https://www.nytimes.com/2017/03/29/health/fda-nominee-scott-gottlieb-recuse-conflicts.html).
[492] *Id.*
[493] Egilman Report at § 7.201.
[494] Egilman Exhibit B.201.
[495] Egilman Report at § 7.349.
[496] For this same reason, Dr. Egilman's opinion that, because the FDA required that application holders participate in and support the REMS, "the FDA placed the convicted criminal and FDA rule breakers in charge of the chickens" is nonsensical and betrays a fundamental misunderstanding of REMS and the FDA. *See* Egilman Report at § 7.383; Egilman Exhibit B.383.

Defendants) "leveraged the REMS plan to prioritize the treatment of pain over the danger of addiction and abuse," Dr. Egilman sets out no evidence of such.[497] Rather, as noted above, the REMS Blueprint fully sets out the risks of addiction, among others. *See supra* § X. Dr. Egilman's assertion otherwise is baseless.

"Opinion" 7.462. Dr. Egilman writes that the FDA timeline of some of its opioid-related efforts that I describe above "omits regulatory capture."[498] Yet, Dr. Egilman does not explain what is meant by "regulatory capture," and nowhere does he set out any evidence of any "regulatory capture" by or related to Allergan.

* * *

In sum, Dr. Egilman's attempt to denigrate the FDA and the work it does, and to suggest that Allergan had any inappropriate relationship with the FDA, is unsupported by the evidence. As I have set out throughout this report, the FDA has done an enormous amount of work to ensure the safety and efficacy of opioid medications, and I have seen no evidence that Allergan influenced it in any improper way. Dr. Egilman offers no evidence otherwise.

[497] Egilman Exhibit B.349 (citing Acquired_Actavis_00656038; Acquired_Actavis_00655879). Dr. Egilman states in Exhibt B.349 that a reference in one of those documents to tickets to a REMS meeting as "golden tickets" "indicat[es] the value of meeting with the FDA to progress the company's goals." *Id.* This conclusion is misleading and wholly unsupported.
[498] *See* Egilman Report at § 7.462.

Carl C. Peck

Date: May 10, 2019

Dr. Carl Peck

EXHIBIT A - DOCUMENTS CONSIDERED

I. Documents Cited/Referenced in Body of Report

Referenced throughout report above.

II. Depositions and Deposition Exhibits for the Following Witnesses

Altier, Jennifer - August 2, 2018
Baran, Nancy - December 11, 2018
Barrett, Jeannette - November 2, 2018
Boothe, Doug - January 17, 2019
Clarke, Michael - December 7, 2018
Dorsey, Michael - January 8, 2019
Egilman, David S. - April 25-26, 2019
Galant, Rachelle - January 15, 2019
Kaufhold, Stephan - October 26, 2018
Kessler, David - April 25-26, 2019
Leitch, Nathalie - January 22, 2019
McCormick, Jinping - January 9, 2019
Myers, David - December 13, 2018
Napoli, Tom - January 17, 2019
Nataline, Terri - December 13, 2018
Perfetto, Michael - December 18, 2018
Snyder, Julie - November 2, 2018
Thapar, Sarita - January 10, 2019
Woods Mary - January 9, 2019 (30(b)(6)) and January 10, 2019 (Fact)

III. Expert Reports and Materials from the Following Plaintiff Experts

David Kessler
David S. Egilman

IV. Case Materials

Allergan's Objections and Responses to Plaintiffs' First, Second and Third Sets of Interrogatories in *In re: National Prescription Opiate Litigation* (Track One cases)
Allergan's Written Responses to Topics in Plaintiffs' Amended Notice of Deposition Pursuant to Rule 30(b)(6) in *In re: National Prescription Opiate Litigation* (Track One cases)
Second Amended Corrected Complaint, *The County of Cuyahoga, Ohio v. Purdue Pharma L.P., et al.*
Third Amended Complaint and Jury Demand, *The County of Summit, Ohio v. Purdue Pharma, L.P., et al.*
Any others cited throughout this report.

V. Additional Materials

21 C.F.R. 10
21 C.F.R. 10.30
21 C.F.R. 20.64
21 C.F.R.. 58
21 C.F.R. 200.200
21 C.F.R. 201.56
21 C.F.R. 201.57
21 C.F.R. 202.1
21 C.F.R. 208.1
21 C.F.R. 208.2
21 C.F.R. 208.20
21 C.F.R. 208.24
21 C.F.R. 208.26
21 C.F.R. 312.21
21 C.F.R. 312.23
21 C.F.R. 312.33
21 C.F.R. 314
21 C.F.R. 314.105
21 C.F.R. 314.110
21 C.F.R. 314.125
21 C.F.R. 314.150
21 C.F.R. 314.50
21 C.F.R. 314.70
21 C.F.R. 314.80
21 C.F.R. 314.81
21 C.F.R. 314.94
21 C.F.R. 314.98
21 C.F.R. 320
21 C.F.R. 601.12(f)(2)-(3)
21 C.F.R. Part 1308 Schedules of Controlled Substances: Rescheduling of Hydrocodone Combination Products from Schedule III to Schedule II, Federal Register Volume 79, No.163, available at https://www.deadiversion.usdoj.gov/fed_regs/rules/2014/fr0822.htm
21 U.S.C. 332
21 U.S.C. 333
21 U.S.C. 334
21 U.S.C. 335
21 U.S.C. 352
21 U.S.C. 355
21 U.S.C.A. 355-1
63 Fed. Reg. 66378, available at https://www.govinfo.gov/app/details/FR-1998-12-01/98-31627
71 Fed. Reg. 3922, available at https://www.federalregister.gov/documents/2006/01/24/06-545/requirements-on-

content-and-format-of-labeling-for-human-prescription-drug-and-biological-products

73 Fed. Reg. 49603 at 49604.About FDA Product Approval, available at https://www.fda.gov/newsevents/productsapprovals/ucm106288.htm

Abbreviated New Drug Applications and 505(b)(2) Applications, Fed. Reg. Vol. 81, No. 194 (Oct. 6, 2016), available at https://www.govinfo.gov/content/pkg/FR-2016-10-06/pdf/2016-22690.pdf

Abbreviated New Drug Application Regulations, 57 FR 17950-01, Rules and Regulations (April 28, 1992)

About the Center for Drug Evaluation and Research, available at https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/default.htm

Abuse Potential and Risk of Life-Threatening Respiratory Depression, available at www.rxpatrol.com/pdf/opioid-important-safety-information.pdf

A Brief Overview of Risk Evaluation & Mitigation Strategies (REMS), FDA Basics Webinar, available at https://www.fda.gov/aboutfda/transparency/basics/ucm325201.htm

About FDA, available at https://www.fda.gov/AboutFDA/WhatWeDo/default.htm.

Acetaminophen & Hydrocodone Bitartrate Label, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/040148s053lbl.pdf

A Difficult Balance- Pain Management, Drug Safety, and the FDA, New England Journal of Medicine, available at https://www.nejm.org/doi/full/10.1056/NEJMp0908913

April 16, 2014 FDA Letter, available at https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2014/020616Orig1s051ltr.pdf

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Other materials and documents cited throughout this report.

EXHIBIT B - CURRICULUM VITAE

Carl C. Peck, M.D., Dr. h.c. (Uppsala)

Adjunct Professor, UCSF

Founder and Chairman, NDA Partners LLC

PERSONAL INFORMATION:

Home office address: 5955 Balm Ridge Way
San Luis Obispo, CA 93401
Tele: 805 541-2581; cell: 202 427-7660

Academic address: Department of Bioengineering and Therapeutic Sciences
Schools of Pharmacy and Medicine
University of California at San Francisco

Date of Birth: March 28, 1942

Place of Birth: Kansas

LICENSURE: Medicine and Surgery - State of California, 1971-present

CERTIFICATION: National Board of Medical Examiners, 1969
American Board of Internal Medicine, 1975
American Board of Clinical Pharmacology, 1990

EDUCATION:

High School: Concordia High School, Concordia, Kansas 1960

Undergraduate: University of Kansas, Lawrence, Kansas
B.A., Mathematics/Chemistry 1963
Technische Hochschule, Stuttgart, Germany
Fulbright Grant (Chemistry, German), 1963-1964

Medical School: University of Kansas Medical Center, Kansas City, Kansas
M.D. - 1968

Internship: USA Tripler General Hospital
Honolulu, Hawaii; 1968 - 1969 (Rotating)

Residency: Letterman General Hospital
Presidio of San Francisco, California
1969 - 1972 (Internal Medicine)
Chief, Medical Resident, 1972

Fellowship: Research Fellow
Division of Clinical Pharmacology

Dr. K.L. Melmon, Chief
Lewis Sheiner, Faculty Advisor
University of California Medical Center
San Francisco, CA, 1972 - 1974

PROFESSIONAL EXPERIENCE:

Research Assistant, Nuclear Physics
Department of Nuclear Physics
Dr. L.W. Seagondollar, Chief
University of Kansas, 1960 - 1962
Lawrence, KS

U.S. Army Medical Corps, 1967-1990, Colonel 1981 – 1990

U.S. Public Health Service, 1990 - 1993; Rear Admiral (08)

Tropical Medicine
U.S. Army Medical Research Unit
Kuala Lumpur, Malaysia, 1972

Research Clinical Pharmacologist
Blood Research Division
Department of Surgery, Letterman Army Institute of Research
(1 July 1974 - 1 July 1977)

Department of Medicine, Clinical Instructor
Division of Clinical Pharmacology
University of California Medical Center
San Francisco, CA, 1974-1976

Clinical Assistant Professor of Medicine
Department of Medicine
Division of Clinical Pharmacology
University of California Medical Center
San Francisco, CA, 1976-1980

Chief, Division of Blood Research
Letterman Army Institute of Research (LAIR)
Presidio of San Francisco, CA
(July 1977 - January 1980)

Adjunct Associate Professor of Medicine and Pharmacology: 1978- 1979; Associate Professor: 1980-1982; Professor: 1982-1987
Uniformed Services University of the Health Sciences (USUHS)
Bethesda, MD

Director, Division of Clinical Pharmacology 1980 - 1987
USUHS

Attending Physician, Department of Medicine,

Walter Reed Army Medical Center 1980 - 1987
Naval National Medical Center 1980 - 1981

Director, Center for Drug Evaluation and Research
Food and Drug Administration
Rockville, Maryland 1987 - 1993

Boerhaave Professor of Clinical Drug Research
Leiden/Amsterdam Center for Drug Research
Leiden University
Leiden, The Netherlands 1993 - 1995

Professor of Pharmacology and Medicine (Clinical Pharmacology)
Founder and Director, Center for Drug Development Science (CDDS)
Georgetown University Medical Center
12 September 1994 – 15 October 2004

Adjunct Professor of Pharmaceutical Sciences – 2004-present
Director, Center for Drug Development Science (15 October 1994 - 1 September, 2006)
Department of Bioengineering and Therapeutic Sciences
Schools of Pharmacy and Medicine
University of California at San Francisco

Visiting Professor, Peking University, Beijing China (2009 – present)

HONORS & AWARDS:

Department of Army Research and Development Award for 1978 (for contributions to the multi-clinic cooperative clinical trial of the CPDA-1 blood preservative system)
Meritorious Service Medal, U.S. Army, 1980
USA Medical Corps "A-prefix", 1984
The Defense Superior Service Medal, U.S. Army, 1988
Outstanding Service Medal, U.S.P.H.S., 1989
Distinguished Service Medal, U.S.U.H.S., 1991
Outstanding Unit Citation (ddI Group, FDA), 1992
Commissioner's Special Citation, (CANDA Group), 1993
PHS Meritorious Service Medal, 1993
FDA Distinguished Career Service Award, 1993

Rawls Palmer Progress in Medicine Award, ASCPT, 1994

Australian Society for Clinical & Experimental Pharmacology
Visiting Professor 11/30 - 12/22/85 (lectured at universities in Auckland, New Zealand; and Brisbane, Sidney, and Melbourne, Australia)

Consultant in Clinical Pharmacology to U.S. Army Surgeon General, 1986 - 1990

St. Vincent's Hospital Visiting Professor (Sidney, Australia) Oct. 1-3, 1986, Rutgers University, Department of Pharmaceutics, Visiting Professor, Sept. 21, 1988

University of Toronto, Division of Clinical Pharmacology, Visiting Professor, Jan. 17, 1989

Sidney Riegelman Memorial Lectureship, University of California, San Francisco, April 27 - May 1, 1992

Boehaave Professorship, Leiden University, Leiden, The Netherlands, 1993-1994
Inaugural lecture: Clinical new drug development: how golden are the eggs?"

Sir Henry Hallett Dale Memorial Lecture, The Johns Hopkins University School of Medicine, Baltimore, November 7, 1995.

Thomas E. Hanrahan Memorial Lecture, Pharmaceutical Research and Manufacturers of America Foundation, Washington, DC, February 19, 1998.

Honorary Fellow, American College of Clinical Pharmacology. September 25, 1998.

FDA Distinguished Alumni Award, June 11, 1999

Honorary Doctorate Degree – University of Uppsala (Sweden) conferred the honorary doctorate degree (Doctor Honoris Causa) to Dr. Peck in January 2002 in recognition of "outstanding contributions to the science of drug development".

"Candlelight Lecture" – Myths, Maths, and Medicines. Swedish Academy of Pharmaceutical Sciences, 2006 Roseno Conference, August 25, 2006.

"Lewis B. Sheiner Memorial Lecture", First American Conference on Pharmacometrics, Tucson, AZ March 10, 2008.

2009 Henry W. Elliott Distinguished Service Award, American Society for Clinical Pharmacology and Therapeutics, March 18, 2009.

2009 Visiting Scholar, American Industrial Health Council (AIHC) Hamner Institutes, Research Triangle Park, North Carolina. September 8-9, 2009.

2010 Visiting Scholar and Keynote Lecturer, Annual Chapel Hill Drug Conference "Quantitative Pharmacology", May 13, 2010

2011 Special Recognition Award, Association of Clinical Research Professionals and Association of Pharmaceutical Physicians and Investigators, Seattle, Washington April 30, 2010

2012 ASCPT Gary Neil Prize for Innovation in Drug Development. Presented at Annual ASCPT Meeting in Baltimore, MD, March 14, 2012

2014 Nathaniel T. Kwit Memorial Distinguished Service Award, presented at Annual ACCP Meeting, September 14, 2014.

2017 Sheiner–Beal Pharmacometrics Award at the 118th Annual Meeting of the American Society for Clinical Pharmacology and Therapeutics (ASCPT), March 15–18, 2017, in Washington, D.C. (Announced October 2016).

2018 Gary Levy Memorial Lectureship, SUNY at Buffalo University, Buffalo, NY

PROFESSIONAL SOCIETIES:

American College of Physicians Associate, 1973-1974
Member: 1976 - 1979
Fellow: 1979 - present

American Federation for Clinical Research, 1974 - 1993
American Association for the Advancement of Science, 1976 - 1993

American Society for Clinical Pharmacology and Therapeutics, member, 1974 - present; President, 1998-1999

American Society for Pharmacology and Experimental Therapeutics, 1980 - present

Delegate to U.S. Pharmacopeia Convention, September 2, 1980 - 1985

Skin Pharmacology Society, 1985 - 1993

American Association of Pharmaceutical Scientists, 1986 - present; Fellow: 1991 - present

American Academy of Pharmaceutical Physicians, Fellow: 1995 - present

PUBLIC SERVICE:

Editorial Board Membership Rational Drug Therapy, 1984 - 1987
Modeling Methodology Forum (Am. J. Physiology) 1985 - 1987
Clinical Pharmacology and Therapeutics, 1985 - present
Skin Pharmacology Society Journal, 1986 - 1993

Journal Reviewer

Am. Journal of Physiology
Journal of Clinical Nutrition
Annals of Internal Medicine
Clinical Pharmacokinetics
Clinical Pharmacology and Therapeutics
International Journal of Pharmaceutics
J. Controlled Release
J. Pharmaceutical Sciences
J. Theoretical Biology
Journal of Pharmacokinetics and Biopharmaceutics
New England Journal of Medicine
Pharmaceutical Research Science Transaction
Transfusion
Vox Sanguinis

Professional & Society Activities

American Association of Blood Banks Committee on Transfusion-Transmitted Diseases, 1982-1983Scientific Program Committee, 1983-1984

American Association of Pharmaceutical Scientists Science Policy Committee, 1996 - present

American Society for Clinical Pharmacology and Therapeutics
Delegate to AAMC Council of Academic Societies, 1983-1987
Scientific Program Committee 1981 - 1982; Vice Chairman 1984-1985, Chairman 1986
ASCPT/ASPET Liaison Committee on Clinical Pharmacology 1981- 1982, Chairman, 1983 - 1985
CPT-83 Organizing Committee 1981 -1983, Chairman
Satellite Meeting Subcommittee
Education Committee 1984 - 1985
Finance Committee 1982 - 1985
Long-Range Planning Committee 1986 - 1990, 1995 - 1996

Vice President, 1986-87, 1994
Board of Directors, 1982 - 1999
President, 1998-1999
Food and Drug Law Institute, Board of Trustees, 1995 – 2003

European Center for Pharmaceutical Medicine (ECPM) Advisory Board, 1995 – present

Founder, Faculty. American Course in Drug Development and Regulatory Science (ACDRS – Washington DC and San Francisco), 2007-present

Founder, Faculty. China. Course in Drug Development and Regulatory Science (CCDRS – Beijing, China), 2009 - present

COMMERCIAL SCIENCE ADVISORY BOARDS (SAB), AND BOARDS OF DIRECTORS (BD)

SAB (Chairman, Clinical Pharmacology), Therapeutic Discovery Corporation, Palo Alto – 1994-1999

SAB (Chairman, Regulatory Affairs), Alza Corporation – 1995 - 1999

SAB (Chairman) Pharmaceutical Research Associates, Vienna VA – 1995 - 2001

BD, Ligand Pharmaceuticals, San Diego – 1997 – 2005

BD (Founder), Dermal Systems International (DSI, S. San Francisco – 1986 – 2003

SAB, Aardex Corp, Zug, Switzerland – 1998 – present

SAB, Depomed, Redwood City, CA – 1998 - 2002

SAB, Guilford Pharmaceuticals, Baltimore – 1999 – 2003

SAB, Inhale Therapeutic Systems, San Carlos – 1999 – 2004

SAB, RealAge, San Diego – 1999 – present

SAB, Pharsight Corporation, Palo Alto, CA – 1999 - 2002

BD, DermTech, San Diego – 2001 – present

BD (Founder, Chairman), NDA Partners LLC, Rockville, MD – 2003 – present

Schering-Plough Corporation – Member Science and Technology Committee – 2006-2009

SAB, Certata/SimCyp Corporation, Manchester England – 2008 – 2015

SAB, UCB Pharmaceuticals, Brussels Belgium. 2009-2017

AB, UCSF-Stanford FDA-funded Center of Excellence in Regulatory Science (CERSI) 2017-present

Review Boards & Study Section Activities:

NIGMS Pharmacology Study Section - Ad Hoc Reviewer, 1980, 1981
NIH/DRR Special Study Section - Chairman, 1981
USAMRDC Advisory Panel, Member of Pharmacology (WRAIR) & Blood (LAIR) Subcommittees, 1982 - 1985
NIH/Small Business Grants Review Board, 1983, 1985
NIH, Pharmacology Study Section, 1984 - 1987
American Board of Clinical Pharmacology, Charter Board Member, 1989 - present

UNIVERSITY SERVICE

Chairman, USUHS Human Subjects Review Board 1982-1984
USUHS Automated Information Systems Policy Committee, 1984-1986

Member, Georgetown University Medical Center Executive Advisory Council, 1997-1999

Acting Director, NIGMS Clinical Pharmacology Training Grant, 2001 – 2003

TEACHING ACTIVITIES:

Conversational German
Experiment in International Living
Putney, Vermont, 1965

Clinical Pharmacology and Therapeutics:
Medical Students, University of California Medical Center, 1972-1980
House-staff, Letterman General Hospital and University of California, 1972-1980
Uniformed Services University, 1979-1993
Introduction to Statistics for Research Workers: (3-part lecture series)
Department of Experimental Surgery
Letterman Army Institute of Research, 1974 - 1980

USUHS Division of Clinical Pharmacology, 1980 - 1987

Elementary Pharmacokinetics, USUHS PH0501, and CDER, FDA, 1980 - 1992

Advanced Pharmacokinetics, USUHS PH0502, and CDER, FDA, 1981 - 1993

Advanced Pharmacokinetics Seminar, USUHS PH0503, 1984

Bedside Techniques in Clinical Pharmacokinetics, 1981 - 1986

Boerhaave Lecture Series in Advanced Methods in Clinical Drug Testing, Leiden University, The Netherlands, 1994

Many courses, workshops, lectures at FDA, Rockville, MD 1987 – 2011

Cofounder and Lecturer in American Course in Drug Development and Regulatory Science, Washington DC 2007 – present; San Francisco 2008 – present

Cofounder and Lecturer in China Course in Drug Development and Regulatory Science, Beijing, China 2009 – present

Cofounder, Planning Committee Member, Presenter in the Pacific Coast Statisticians and Pharmacometricians Innovation Conference (PaSiPHIC), San Luis Obispo, CA – 2010 – present

Faculty, NIH Clinical Pharmacology Course, 1997 – present

Faculty, NIH Clinical Pharmacology Course, Kulakov Institute, Moscow, Russia May 13-17, 2013

Graduate Students and Post-doctoral Trainees Supervised:

N. Stambler, M.S.	1980-81
E. Perlin, M.D.	1980-81
J. Berenberg, M.D.	1981-82
L. Mell, Ph.D.	1981-83
D. Ezra, M.D.	1981-84
R. Platzer, M.D.	1982-83
S. Perkins, M.D.	1983-83
M. Shmuklarsky, M.D.	1982-84
B. Chen, M.D.	1983-84
N. Haim, M.D.	1984-86
V. Hill, M.D.	1985-87
N. Fleischer, (Ph.D.)	1985-88
C. Lehmann, Pharm.D.	1986-87
G. Murphy, M.D.	1986-88
C. Bradley, Ph.D.	1986-88
R. Brueckner, M.D.	1988-90

S. Rinsler	1989-92
B. Tuk	1993-94
H. Kimko	1995-97
J. Gobburu	1997-99
J. Li	1998-00
Teruki Ehara	1998-00
I. Jang	1998-00
R. Bies	1998-00
M. Staschen	2000-02
H. Lee	2000-02
M. Shibatsuji	1999-01
J. Cross	1999-01
A. Westelinck	2000-01
H. Kraiczi	2000-01
S. Tannenbaum	2001-03
S. Berry	2002-04
C. Garnett	2002-04
D. Yim	2003-05
B. Green	2004-05
T. Vu	2005-07
R. Crombag	2007-08

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1. "Modernizing Effectiveness Testing in Drug Development." FDA Reform Legislation, Hearings Before The Committee on Labor and Human Resources, United States Senate. Washington, DC, February 21, 1996.
2. "Streamlining and Modernizing Drug Development." FDA Reform Legislation, Hearings Before The Subcommittee on Health and Environment of the Committee on Commerce, United States House of Representatives. Washington, DC, May 2, 1996.
3. "Clinical Drug Development May Soon be accomplished in Less that 3 Years: Will FDA and the Pharmaceutical Industry be Ready?" Reauthorization of the Prescription Drug User Fee Act and FDA Reform, Hearings before the Subcommittee on Health and Environment, Committee on Commerce, United States House of Representatives. Washington, DC, April 23, 1997.

4. Statement of Dr. Carl Peck, U.S. Department of Health and Human Services, Secretary's Task Force on Drug Importation, "stakeholder meeting discussion that will focus on the international, and academic perspectives on issues related to importation", Rockville, Maryland, April 27, 2004

Issued Patents

1. Dermal Substance Collection Device (U.S. No. 4,706,676, issued 11/17/87) Canadian No. 1251106.
2. Method of Dermal Substance Collection (U.S. No. 4,819,645, divisional of 4,706,676; issued 4/11/89).
3. Gelled Composition (U.S. No. 4,960,467, divisional of 4,706,676; issued 10/2/90).
4. Transdermal Vapor Collection Device (U.S. No. 4,909,256, continuation-in-part of 4,706,676, issued 3/20/90; Japanese Publication No. 2-503155, 10/4/90; European Publication No. 347,447, 12/27/89).
5. Transdermal detection System (U.S. No. 4,821,733, issued 4/18/89; European Publication No. 574,799; Japanese Publication No. 1-163666, 6/27/89).
6. Laser-enhanced Transdermal Substance Collection (U.S. App. S.N. 07/544,304, filed June 27, 1990; continuation-in-part of 4,960,467; owned jointly by DSI (under license from U.S. Army) and another entity.
7. Systems and Methods for Monitoring Health and Delivering Drugs Transdermally (US. App. S.N. 60/208,327, submitted June 1, 2000; filed May 30, 2001, Serial No.: 866826).; jointly owned by DSI, Georgetown University, and SAIC. US. Patent Application No. 20030225362, published December 4, 2003. Issued May 3, 2005 – No. 6,887,202.
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9. Currie, John F….Peck, Carl C. Systems and methods for monitoring health and delivering drugs transdermally. US 6,887,202 B2, May 30, 2005).
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11. Regan, Jeffrey F., Miller, Randal, Peck C. High Throughput Methods and Devices for Assaying analytes in a fluid sample. US 2004/0002121, January 1, 2004).
12. Currie, John F….Peck, Carl C. Systems and methods for monitoring health and delivering drugs transdermally. US 8,568,15 B2, October 29, 2013).

EXHIBIT C - PRIOR TESTIMONY

I have testified as an expert at trial or deposition in the following cases over the prior four years:

- June 11, 2015. Trial. *Helsinn Healthcare S.A., et al. v Dr. Reddy's Laboratories, Ltd., et al.*, No. 11-CV-03962 (MLC) (DEA), 11-CV-00579 (MLC) (DEA) (Consolidated) (D.N.J.).

- February 16, 2016. Deposition. *Hartley v. Nova Law, MD, et al.*, No. CV 11-903122, Circuit Court for Jefferson County, Alabama.

- July 21, 2017. Deposition. *AstraZeneca Pharmaceuticals LP, et al. v. Teva Pharmaceuticals USA, Inc., et al*, No. 1:15-cv-06039-RMB-KMW (D. Del.).

- August 11, 2017. Deposition. *In re: Celexa and Lexapro Marketing and Sales Practices Litigation*, MDL No. 2067 (D. Mass.).

- March 29, 2019. Deposition. *Perrigo Co., et al. v. United States of America*, No. 1:17-cv-737.